FDA Briefing Document

Risk Communication Advisory Committee Meeting

June 8 and 9, 2015

Communicating Information about Fetal Effects in Product Labeling for Methadone and Buprenorphine Maintenance Therapy for Opioid Addiction, and the Maternal Benefits and Risks of Treatment, to Best Enable Patients and Providers to Make Informed Decisions about the Use of These Drugs during Pregnancy

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of how best to communicate the benefits and risks of methadone and buprenorphine treatment of opioid addiction during pregnancy to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Food and Drug Administration
Center for Drug Evaluation and Research

Risk Communication Advisory Committee

Communicating Information about Fetal Effects in Product Labeling for Methadone and Buprenorphine Maintenance Therapy for Opioid Addiction, and the Maternal Benefits and Risks of Treatment, to Best Enable Patients and Providers to Make Informed Decisions about the Use of These Drugs during Pregnancy

June 8 and 9, 2015

Briefing Materials
Table of Contents

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products

MEMORANDUM

Date: May 22, 2015

From: Sharon Hertz, MD
Division Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

To: Chair, Members, and Invited Guests

Re: Overview of the June 8-9, 2015 Meeting of the Risk Communication Advisory Committee to discuss approaches to communicating information about fetal effects in product labeling for methadone or buprenorphine maintenance therapy for opioid addiction, and about the maternal benefits and risks of treatment, to best enable patients and healthcare providers to make informed decisions about the use of these drugs during pregnancy.

Over the last few years, neonatal abstinence syndrome (NAS), a term which includes neonatal opioid withdrawal syndrome (NOWS), as well as neonatal withdrawal from other drugs, has garnered a great deal of attention from Congress, the States, and the medical community as the incidence of the condition has increased. In September 2013, FDA required a boxed warning for the class of extended-release and long-acting (ER/LA) opioid analgesics to describe the risk of NOWS. Shortly thereafter, FDA received a citizen petition in October 2013 from the National Advocates for Pregnant Women (NAPW) objecting to the planned changes. Many of the objections pertained to the use of opioids as maintenance treatment for addiction, rather than as analgesics. FDA issued a response to the citizen petition on April 16, 2014. Since the issuance of the response to the citizen petition, FDA has given additional consideration to the complexities of the potential impact of the labeling for the medication-assisted treatment of opioid addiction regarding NOWS. As FDA approaches revising the labeling of NOWS in the product labeling for the opioids approved for the treatment of opioid addiction, FDA seeks the advice of the Risk Communication Advisory Committee on how best to communicate the benefit of medication assisted therapy for opioid addiction during pregnancy and the risk of NOWS.

The document that follows will provide the background and regulatory history for the opioids approved for the treatment of opioid addiction; summarize the labeling action taken by FDA on NOWS for the ER/LA opioid analgesics; summarize FDA's response to the concerns raised by the NAPW citizen petition; briefly describe other safety issues under review for the opioids approved for opioid addiction; and describe the regulatory requirements and guidance recommendations for the sections of labeling relevant to this safety issue.

The briefing package also includes the following background information:

- National Advocates for Pregnant Women (NAPW) Citizen Petition
- FDA response to the NAPW Citizen Petition
- 2012 American College of Obstetricians and Gynecologists Committee Opinion on Opioid Abuse, Dependence, and Addiction in Pregnancy (link to document)
- 2012 American Academy of Pediatrics Clinical Report on Neonatal Drug Withdrawal (link to document)
- FDA Guidance: Drug Safety Information – FDA's Communication to the Public
- Examples of approved product labeling for opioids approved for treatment of opioid addiction

At the meeting, you will be asked to discuss approaches to communicating about the issues outlined above, as well as anticipating potential unintended consequences of such communication, and strategies for minimizing unintended consequences.

Again, we are grateful for your participation in this meeting and thank you for providing your expertise and insight. We are hopeful that your discussions and deliberations at this meeting will assist us in determining possible regulatory options, including, but not limited to, changes to the product labeling, as well as ideas for communicating outside of the regulatory framework.

Draft Points to Consider

Neonates exposed to either illicit or therapeutically administered opioids in utero are at risk for NOWS. NOWS is a condition which may be life-threatening if not recognized and treated. The serious adverse reaction of unrecognized and untreated NOWS can be prevented or reduced in frequency or severity with careful monitoring and clinical management. According to FDA labeling guidance, such a risk may be suitable for communication in a boxed warning in the labeling of opioids approved for treatment of opioid addiction.

Opioid addiction is a condition for which treatment may be stigmatized and even criminalized. Patients may be ambivalent about seeking treatment during pregnancy, despite medication assisted treatment with methadone or buprenorphine having been shown to improve outcomes for mothers and neonates. Following the addition of a boxed warning for NOWS to the labeling for opioids prescribed for chronic pain, a number of stakeholders expressed concern that the warning would adversely affect women's access to treatment during pregnancy. Specifically, boxed warnings for drug products with indications for the treatment of addiction may affect patient, prescriber, and societal perceptions of the acceptability of treatment.

1) Given the scenario described in the two paragraphs above, how and where do we most effectively communicate the risk of NOWS in light of the demonstrated benefits of medication assisted therapy during pregnancy?

- In product labeling (e.g., boxed warning, Warnings and Precautions, Specific Populations)
- Via other communication tools

2) Discuss the potential effects of various communication approaches on the following:

- Patient acceptance and adherence to treatment
- Physician willingness to treat patients
- Health care system policies
- Legal repercussions for mothers

Discuss any additional unintended consequences that may occur.

3) Discuss communication strategies that FDA can use to minimize adverse unintended consequences. Discuss the role other government agencies, professional organizations, or patient advocacy groups can play in facilitating communication of the balance of risk and benefit and mitigating potential adverse unintended consequences.

4) As we continue to monitor the safety profile of these products, we may need to communicate in the future about other adverse effects. Discuss the general principles of communicating risks of these products in the setting of pregnant women on medication assisted therapy to maintain a balanced assessment of the benefit and risk.

Communicating Information about Fetal Effects in Product Labeling for Methadone and Buprenorphine Maintenance Therapy for Opioid Addiction, and the Maternal Benefits and Risks of Treatment, to Best Enable Patients and Providers to Make Informed Decisions about the Use of These Drugs during Pregnancy

Integrated Summary Memo

Table of Contents

1 Introduction

Over the last few years, neonatal abstinence syndrome (NAS), a term which includes neonatal opioid withdrawal syndrome (NOWS)[1], as well as neonatal withdrawal from other drugs, has garnered a great deal of attention from Congress, the States, and the medical community as the incidence of the condition has increased. FDA has also become aware of the increasing incidence of NAS. An assessment of a nationally representative Agency for Healthcare Research and Quality database published in 2012 showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12- 3.67) per 1000 hospital births per year (P for trend < .001).[2] The same study documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001]). More recently, the United States Government Accountability Office (GAO) published a report entitled "Prenatal Drug Use and Newborn Health"[3] describing how federal agencies have addressed prenatal opioid use and NAS and recommending that the Office of National Drug Control Policy document the process for developing action items on prenatal opioid use and NAS and that the Department of Health and Human Services designate a focal point to lead departmental planning and coordination on these issues.

FDA has regulatory purview over certain aspects of the drugs approved to treat opioid addiction, specifically:

- the review and approval of marketing applications;
- the monitoring of post-marketing safety; and
- the determination that the labeling and marketing of such products is truthful and not misleading

Additionally, FDA has been an active participant in Federal efforts to ensure the safe use of prescription drugs with the potential for abuse and drugs for the treatment of drug dependence. The function of product labeling is to communicate the essential scientific information needed for the safe and effective use of the drug. Some labeling may be particularly challenging to draft because of the larger societal implications of the benefits and risks of a medication, particularly during pregnancy when the fetus is also exposed to the drug or drugs a mother is taking. FDA is seeking the input of the Risk Communication Advisory Committee to assist in communicating

[1] The condition referred to as neonatal abstinence syndrome (NAS) refers to the phenomenon whereby a neonate withdraws from substances he/she was exposed to during gestation because of substances taken by the mother. However, NAS may refer to any drug from which a neonate may be withdrawing (e.g., benzodiazepines, opioids, selective serotonin reuptake inhibitors [SSRI]). Because we are focused on neonatal opioid withdrawal at this meeting, we are using the term "neonatal opioid withdrawal syndrome" (NOWS).
[2] Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. JAMA 2012; 307 (18): 1934-30.
[3] http://www.gao.gov/products/GAO-15-203

about the risk of NOWS recognizing the significant benefit to mothers and babies accrued when pregnant women with opioid addiction use medication assisted treatment.

2 Medications Approved for Treatment of Opioid Addiction

2.1 Methadone

Methadone is a μ-opiate receptor agonist with unusual pharmacologic properties, such as a long duration of action attributable to slow accumulation and slow elimination. Methadone (Dolophine) was initially approved for marketing in 1947 as an analgesic under the then-prevailing law, which required only the demonstration of safety under the 1938 Federal Food, Drug, and Cosmetic Act (FD&CA). After the 1962 amendments to the FD&CA adding the requirement for demonstration of efficacy, methadone was reviewed by the National Academy of Sciences Panel on Drugs for Relief of Pain as part of the Drug Efficacy Study Implementation (DESI) process. The DESI notice for methadone was published on August 26, 1970, and found methadone to be effective for three indications

1. treatment of moderate to severe pain
2. control of cough in those patients for whom antitussives with less abuse liability have proven inadequate
3. "for suppressing the narcotic abstinence syndrome in the course of withdrawal therapy for narcotic dependence."

The third indication allowed for use of methadone in short-term "detoxification" treatment. However, this use was constrained, as noted below, by the Harrison Act of 1914.

The provision of opiates to opiate-dependent patients to maintain their dependence was deemed illegal in the U.S. under the Harrison Act of 1914. In the early 1960's, during a resurgence of heroin use and heroin-related crime and overdose deaths, researchers inspired by the British model of allowing physicians to prescribe opiates to addicts began to investigate the utility of maintaining heroin addicts on long-acting pharmaceutical opiates. Primarily using methadone, this work was carried out at first under an investigational new drug application (IND) or without regulatory oversight (as FDA did not then require INDs of individual investigators). Although short-term detoxification treatment of opioid dependence using methadone was considered an established indication under the DESI notice, the maintenance use of methadone for addiction treatment was more controversial. A determination was made that public health would be served by permitting this use of methadone, but also that a restricted distribution system would be necessary to prevent diversion and to ensure the quality of care. In 1972, proposed regulations were promulgated that created a regulatory structure for opioid treatment programs (OTPs), or "methadone clinics." Methadone was to be *dispensed* (not prescribed) under specified conditions in specially-registered programs. Two products with features intended to make them less prone to abuse by the intravenous route, a methadone syrup and a dispersible tablet intended to be dissolved before dispensing, were approved specifically for use in OTPs. All marketing applications for methadone were withdrawn under a Federal Register notice; to resume marketing, manufacturers had to re-submit with revised labeling and supporting data. The

antitussive indication was also revoked at that time. Some holders of approved applications for methadone analgesics submitted supplemental applications to conform with the new labeling requirements and to add the maintenance treatment indication while others remained withdrawn from marketing.

Regulations were promulgated (*see* 21CFR part 291) in 1972 and legislation entitled the Narcotic Addict Treatment Act of 1974 (NATA) was subsequently passed. The NATA amended the Controlled Substances Act to require a separate DEA registration for practitioners and treatment programs engaged in methadone maintenance therapy and obliged programs to comply with standards promulgated by the Secretary of HHS. Under these provisions, opioid treatment programs (OTPs) could *dispense,* but not *prescribe,* specific opioid medications[4] for the treatment of addiction. Initially, an enforcement-based system was overseen by the FDA's Office of Compliance, but this system was replaced by an accreditation-based system (42 CFR Part 8)[5] overseen by the Center for Substance Abuse Treatment (CSAT, a component of the Substance Abuse and Mental Health Services Administration [SAMHSA]) in 2001. Under the regulations, pregnant women are given priority for admission to OTPs, and programs must have "policies and procedures that reflect the special needs of patients who are pregnant. Prenatal care and other gender specific services for pregnant patients must be provided either by the OTP or by referral to appropriate healthcare providers."[6]

Programs are also subject to State regulations.

2.2 Buprenorphine

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain[7], two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence, with several other transmucosal formulations following.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-receptor. Like methadone, buprenorphine's activity at the μ-receptor was expected to relieve patients' urge to use illicit opioids, and like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning. Additionally, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, further deterring abuse of these substances for buprenorphine-maintained patients.

However, due to its partial agonist properties, the euphorigenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased euphorigenic effect that would result from full opioid agonists. A

[4] Originally only methadone, subsequently amended to permit levomethadylacetate (LAAM).
[5] Originally addressed used of methadone and LAAM in OTPs, subsequently amended to include buprenorphine.
[6] 42 CFR 8.12(f)(3).
[7] Buprenex, NDA 18401 Reckitt Benckiser

ceiling effect was also observed for respiratory depressant effects. This resulted in a lower risk of fatal overdose, and was expected to limit its attractiveness as a drug of abuse relative to full agonists.

Because it is a partial agonist, buprenorphine has the potential to precipitate withdrawal symptoms when used by an individual who is dependent on full opioid agonists such as heroin, methadone, or oxycodone. Many buprenorphine products also contain naloxone. The naloxone is intended to be inactive when the product is used as intended, but to add an additional measure of abuse deterrence by precipitating more severe withdrawal if the product is crushed and injected by an individual dependent on full agonists. Current labeling suggests that pregnant women be treated with a product that does not contain naloxone because the effects of naloxone are not well-studied in pregnancy.

When buprenorphine was under development for the treatment of opioid addiction, its pharmacology suggested that it might be appropriate for use outside the OTP setting. In the interest of expanding access to treatment for opioid addiction, the Drug Addiction Treatment Act of 2000, DATA) was passed, which amends the Controlled Substances Act to waive the requirement for separate registration (i.e., as an OTP as called for under the NATA) for practitioners (meeting certain requirements) who wish to prescribe Schedule III-V narcotic drugs that are approved for the treatment of narcotic addiction. The law requires that physicians interested in a waiver must submit a notification that certifies their qualifications and indicates that the physician has the capacity to refer for ancillary services as needed, and agrees to adhere to limits on the numbers of patients treated. To qualify for a waiver, prescribers must meet requirements for training, which can be fulfilled, among other ways, by taking an 8-hour course offered by one of several designated organizations. The law does not address treatment of pregnant women or stipulate the content of the training with regard to treatment of pregnant women.

2.3 Levomethadylacetate (LAAM)

A third medication, levomethadylacetate hydrochloride (also known as levaceytlmethadol, "LAAM") was approved in the US (as Orlaam) in 1993. LAAM is a synthetic opioid analgesic which is structurally related to methadone. It is a pro-drug, which is metabolized to two active metabolites. LAAM was made available through OTPs under the provisions of the NATA and the implementing regulations under 21CFR Part 291, and after 2001, 42CFR Part 8. However, because its pharmacologic properties permitted LAAM to be effective with thrice-weekly dosing, patients could attend the OTP less frequently than was required during methadone treatment.

In December, 1999, a new safety concern (the life-threatening cardiac arrhythmia, torsade de pointes) was identified, leading to the re-labeling of Orlaam to include additional safety warnings (including a boxed warning) and electrocardiogram (ECG) monitoring procedures, and relegation of Orlaam to second-line status. Despite the serious safety concern, the Agency concluded that the drug continued to offer a favorable risk/benefit profile for some patients.

However, subsequently, many OTPs (the only venue in which LAAM was approved for use) made administrative decisions to discontinue offering LAAM to patients, due to the increased burdens of screening and ECG monitoring, and out of concern for liability. Because of the precipitous decline in sales, the manufacturer, Roxane, made a business decision to discontinue marketing of Orlaam. The Agency believed at the time of discontinuation that Orlaam was a medically-necessary product, and continues to view it as a drug with a favorable risk/benefit profile for certain patients. Although the NDA was withdrawn by Roxane, the drug has been relisted in the Orange Book, indicating that FDA would accept new applications referencing the withdrawn product.

3 Labeling for Neonatal Opioid Withdrawal Syndrome in the Extended Release and Long-acting (ER/LA) Opioid Analgesics

The Food and Drug Administration Amendments Act of 2007 gave FDA new authorities in the realm of post-marketing safety. One of these authorities was to be able to require companies to develop and implement a Risk Evaluation and Mitigation Strategy (REMS) when necessary to ensure that the benefits of a drug or biological product outweigh its risks. Because of the misuse and abuse of extended release and long-acting (ER/LA) opioid analgesics that has resulted in a serious public health crisis of addiction, overdose, and death, a REMS was approved for this group of drugs in July 2012. The ER/LA opioid analgesic REMS advances the Agency's goal of improving the safe use of ER/LA opioid analgesics while ensuring continued access to these medications for patients who need them.

Subsequent to the approval of the ER/LA opioid analgesic REMS in 2012, and based on FDA's continued evaluation of the medical literature related to the misuse and abuse of opioid analgesics, FDA determined that the continuing trends of serious risks (including NOWS) related to the use of opioid analgesics warranted modifications to product labeling to more effectively communicate the serious risks associated with ER/LA opioid analgesic use overall, and during pregnancy.

While FDA was drafting the labeling changes described above, the National Association of Attorneys General submitted a letter to the Food and Drug Administration (FDA or Agency) dated May 13, 2013 expressing their concern about the rising incidence of "neonatal abstinence syndrome" due to the increased frequency of neonatal exposure to opioids during pregnancy, and requesting that a "black box warning" be placed on labels of prescription opioid analgesics based on their belief that such a warning "would help ensure that women of childbearing age – as well as their health care providers – are aware of the serious risks associated with narcotic use during pregnancy."

NOWS has long been recognized as a risk to the neonate who is chronically exposed to opioids during gestation. The clinical presentation of NOWS is variable, depending on many factors, including the opioid to which the neonate was exposed in utero, the timing of last exposure prior to delivery, maternal metabolism, neonatal metabolism, and exposure to other licit and illicit substances. Generally, the symptomatology primarily manifests as central nervous system (CNS) irritability, autonomic over reactivity, and gastrointestinal dysfunction.

The labeling for opioid analgesics and opioid agonists/partial agonists approved for treatment of opioid addiction has long included precautionary language for NOWS; however, it has generally been located in the pregnancy section of labeling, a less prominent location than was being requested by the Attorneys General.

In response to the Attorneys General letter, the American Society of Addiction Medicine (ASAM) wrote to the Agency in a letter dated June 19, 2013 to express their disagreement with the recommendations made by the Attorneys General. As stated in the letter, "A 'black box warning' would be intended as a caution to prescribers but it could serve to reduce the number of

opioid addicted pregnant women who are recommended to treatment, the mainstay of which is opioid agonist treatment." They went on to express their concern that the "black box warning" would interfere with pregnant women getting adequate analgesia treatment, stating "There are very few options for the treatment of pain during pregnancy, and opioid analgesics have been relied upon as the safest alternative in conditions requiring treatment for pain. Pregnant women would likely be denied adequate pain treatment if a "black box warning" were placed on these medications."

In September 2013, based on new safety information that FDA articulated in the Safety Labeling Change notification letter[8], FDA determined that a boxed warning for NOWS was appropriate for inclusion in the labeling of the class of ER/LA opioid analgesics, to warn prescribers and patients of the potential risk of NOWS for infants exposed chronically in utero to opioid analgesics. This letter, dated September 10, 2013, includes a boxed warning, a statement in Warnings and Precautions, and a brief mention in the pregnancy section referring back to the other warnings [see Appendix].

Subsequent to the posting of the safety labeling change notification letter for the ER/LA opioid analgesics on September 10, 2013, the Agency received an email from the American College of Obstetrics and Gynecology (ACOG) dated September 16, 2013 conveying concerns similar to those raised by ASAM. The email stated that "The wording from the FDA to manufacture[r]s concerning the warning has the strong potential for those without specialized training to discontinue prescribed LA opioids during pregnancy with possibly fatal results." Additionally, a Citizen Petition (see below) was received expressing concern about the impact of a boxed warning on access to addiction treatment for pregnant women.

It is clear that stakeholders have a range of opinions about how best to alert health care providers and patients to the risk of NOWS, so pregnant women can be appropriately treated and affected neonates can be properly monitored and treated. We recognize the competing health concerns and are seeking the advice of the RCAC to assist FDA in best communicating that balance between the benefits of opioid maintenance treatment for mother and baby with the risk of NOWS.

[8] http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf (page 2)

4 FDA's Response to the Citizen Petition from the National Advocates for Pregnant Women

After an FDA Press Release[9] was issued on September 10, 2013 describing changes to the labeling being required for the ER/LA opioid analgesics, including a boxed warning regarding the risk of NOWS, the Agency received a citizen petition from the National Advocates for Pregnant Women on October 17, 2013, objecting to the planned changes. Many of the objections pertained to the use of opioids as maintenance treatment for addiction, rather than as analgesics. However, the Petitioners also took issue with some of the Agency's conclusions about NOWS.

What follows below is a summary of the Petitioner's arguments, suggestions, and assertions; the full citizen petition is included in the background package.

1. The Petitioners asserted that the NOWS-related warnings were medically inaccurate and that NOWS did not present a serious risk,[10]
2. The Petitioners stated that "The NOWS-related warnings are inconsistent with leading national and international expert opinion on opioid use during pregnancy and other FDA regulations, and fail to consider the negative medical consequences of this labeling for maternal and fetal health," and asked that the Agency modify the full prescribing information to add the following:

   > "Opioid dependent pregnant women should be particularly encouraged to enter treatment since opioid substitution therapy (OST) can lessen the risk of fetal demise and dramatically improve neonatal outcome."
3. The Petitioners asserted that the FDA's conclusion that NOWS is life-threatening was erroneous, and asked that FDA remove the NOWS boxed warning and remove all references to NOWS as "life-threatening" from ER/LA opioid analgesic labeling, including in the medication guide and patient counseling information.[11]
4. The Petitioners argued that NOWS "has not been associated with long-term adverse consequences."[12]
5. The Petitioners expressed concern that "This labeling is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST." [13]

FDA's response to the citizen petitions is provided in the background package. A discussion of certain relevant aspects of the Agency's response follows:

In response to the assertions and requests above, FDA noted that the proposed changes were intended for the labeling of products used as analgesics, and that there are no national or international guidelines regarding the use of opioids for analgesia during pregnancy, other than

[9] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm
[10] *See, e.g.*, docket no. FDA-2013-P-1288 at pp. 3-7.
[11] *See, e.g.*, docket no. FDA-2013-P-1288 at p. 10, *et seq.*
[12] *See, e.g.*, docket no. FDA-2013-P-1288 at pp. 4, 7.
[13] *See, e.g.*, docket no. FDA-2013-P-1288 at p. 11, *et seq.*

for labor analgesia.[14] The impact of untreated pain in pregnancy is not known. The Agency's intent is not to discourage the use of opioids in pregnant women when medically indicated, but rather to provide risk information to inform prescribing and risk-benefit considerations.

Regarding the use of opioid maintenance treatment of addiction, FDA does not oppose national or international guidelines on the treatment of opioid addiction in pregnancy. In 1998, a National Institutes of Health consensus panel recommended methadone as the standard of care for pregnant women with opioid addiction (includes heroin use and misuse of prescription opioid analgesics). More recently, buprenorphine also has been administered to pregnant women as treatment for opioid dependence, based on an accumulating body of medical literature.

National guidelines from the American College of Obstetricians and Gynecologists (ACOG)[15] and the Substance Abuse and Mental Health Services Administration (SAMSHA)[16] and international guidelines from the World Health Organization[17] recommend that pregnant women be treated with methadone or buprenorphine. The rationale for opioid maintenance therapy during pregnancy is to prevent complications of opioid misuse and withdrawal, encourage prenatal care and drug treatment, reduce criminal activity, and avoid risks to the patient of associating with a drug culture.

Heroin use and opioid addiction are associated with an increase in obstetrical complications such as low birth weight, preterm birth, and fetal death.[18,19] According to leading national expert opinion, comprehensive opioid assisted therapy that includes prenatal care reduces the risk of obstetrical complications. National guidelines recommend against withdrawal from opioids during pregnancy because it may be associated with fetal death and a high risk of relapse.

However, FDA disagreed with the addition of specific labeling proposed by the Petitioner recommending that "opioid dependent pregnant women should be particularly encouraged to enter treatment since OST [opioid substitution therapy [sic]] can lessen the risk of fetal demise and dramatically improve neonatal outcome." Although FDA does not oppose this recommendation as a clinical practice guideline, such a statement is not consistent with current labeling policies because clinical practice guidelines are not included in FDA labeling.

Regarding the scientific conclusions about the risks of NOWS, FDA agreed with the Petitioner that NOWS is diagnosable and treatable; however, FDA concluded that NOWS can be life-

[14]American College of Obstetricians and Gynecologists Committee Opinion Obstetric analgesia and anesthesia. Number 36; July 2002.
[15]American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012.
[16]Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. Treatment improvement protocol series 43. Substance Abuse and Mental Health Services Administration; 2005, revised 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK26113.
[17]World Health Organization, Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy (2014).
[18] Minozzi S, Amato L, Vecchi S, Davoli M. .Maintenance agonist treatments for opiate dependent pregnant women. Cochrane Database of Systematic Reviews 2008. Issue 2. Art.No.:CD006318. DOI:10.1002/14651858.CD006318.pub2
[19] Fajemirokun-Odudeyi O, Sinha C, Tutty S, Pairaudeau P, Armstrong D, Phillips T, et al. Pregnancy outcome in women who use opiates. Eur J Obstet Gynecol Reprod Biol 2006; 126(2):170–5.

threatening if it goes unrecognized and therefore untreated. If a mother has not been identified as using opioids (licitly or illicitly) during pregnancy, the infant may not be monitored for the emergence of withdrawal symptoms. If an infant develops NOWS and health care providers do not recognize it, or are not anticipating it, there could be problems with diagnosis or a delay in therapy. Failure to treat NOWS, in turn, could result in unnecessary distress in, and even threaten the lives of, infants who were exposed to opioids in utero. The American Academy of Pediatrics, in a clinical report on neonatal drug withdrawal, stated that, "withdrawal from opioids or sedative-hypnotic drugs may be life-threatening."[20] Other recent studies reflect the same view. For example, Jones, *et al.*, describes the characteristics of neonatal abstinence syndrome (NAS)– a term that includes withdrawal from opioids–by saying, "When left untreated NAS can result in serious illness *(e.g.* diarrhea, feeding difficulties, weight loss and seizures) and death."[21]

The NOWS labeling language added to the labeling for ER/LA opioid analgesics on April16, 2014 states that NOWS is potentially life-threatening **if not recognized and treated,** which represented a clarification of language included in the September 2013 announcement**.** The Agency believes that these clarifying changes more precisely articulate the risks of NOWS. FDA also included this clarifying language to avoid any implication that ER/LA opioid analgesics should never be used during pregnancy due to the risk of NOWS. The Agency agrees that opioid therapy may be necessary for the health and well-being of a pregnant woman. It does not intend to discourage the medically appropriate use of opioids in pregnant women. For example, the boxed warning, and warnings and precautions sections state, "If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available."

FDA disagreed with the Petition's assertions (and proposed labeling statement) that NOWS "is not associated with adverse long-term outcomes." Although data regarding long-term risks of NOWS are limited, and more research is needed, there are suggestions in published literature that NOWS may be associated with substantive long-term effects on neurologic and cognitive functioning.[22] Thus, at present, FDA has not determined that NOWS "is not associated with adverse long-term outcomes."

The FDA noted the Petitioners' concern regarding negative medical consequences for maternal and fetal health due to patient, provider, and societal perceptions of boxed warnings. In recognition of this concern, FDA is convening this Advisory Committee for recommendations regarding appropriate communication strategies.

[20] American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560.

[21] Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31.

[22] *See, e.g.*, Rosen TS and Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age *The Journal of Pediatrics* 1982; 101(2):192-196; Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders *Toxicology Letters* 2003; 140-141:171-181; Wahlsten VS and Sarman **I.** Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatrica* May 2013; 102(5):544-9.

5 Other Safety Issues under Evaluation Relevant to the Opioids approved for Treatment of Opioid Addiction

Some safety issues relevant to the opioid products approved for treatment of opioid addiction have been described in the medical literature, and FDA has begun to evaluate them. No specific regulatory action has been proposed for the safety issues described in this section because they are still under evaluation; however, we are describing them briefly below to make the committee aware of them.

5.1 Neural Tube Defects

As described in a recent FDA Drug Safety Communication dated January 9, 2015[23], FDA reviewed two retrospective case-control studies that reported on opioid exposure in early pregnancy and risk of neural tube defects.[24,25] The studies used interviews to gather information from over 28,000 women on maternal opioid use during pregnancy. Both studies found that mothers of infants with neural tube defects were more likely than mothers of infants without neural tube defects to report opioid use in early pregnancy (aOR=2.2, 95% CI=1.2-4.2; aOR=2.0, 95% CI=1.3-3.2). Although both studies were generally well-designed to assess the association between opioids and neural tube defects, both were susceptible to similar study limitations. In particular, use of maternal interviews could have affected the validity of these studies' findings. For example, mothers of neural tube defect-affected infants may have better recall of opioid exposure during their pregnancies than mothers of infants without birth defects. In addition, mothers of potentially exposed neural tube defect-affected infants may have higher rates of study participation.

Further investigation of this issue is needed before FDA can determine whether the weight of the evidence supports the presence of an increased risk of neural tube defects related to opioid exposure in early pregnancy. The absolute risk of neural tube defects is low in the U.S. at about four to six per 10,000 live births.[26,27] Therefore, if true, a two-fold increased risk would represent a small increase in the absolute risk of neural tube defects.

5.2 Congenital Abnormalities of the Visual System

Congenital abnormalities of the visual system in infants whose mothers took methadone have been reported in the medical literature.[28,29,30,31] Some cases reported methadone as the only drug

[23] http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm
[24] Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 2013;122:838-44.
[25] Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011;204:314.e1-11.
[26] Wallingford JB, Niswander LA, Shaw GM, Finnell RH. The continuing challenge of understanding, preventing, and treating neural tube defects. Science 2013;339:1222002.
[27] Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol 2010;88:1008-16.
[28] Gupta M, Mulvihill AO, Lascaratos G, Fleck BW, George ND: Nystagmus and reduced visual

taken during pregnancy, while others reported concomitant medications, such as benzodiazepines or illicit drugs. Commonly reported events included nystagmus, strabismus, reduced visual acuity, and visual impairment. Although nystagmus clinically improved in some children, complete resolution of the nystagmus was not reported.

acuity secondary to drug exposure In utero: long-term follow-up. J Pediatr Ophthalmol Strabismus 2012; 49(1):58–63.
[29] Hamilton R et al. Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy. British J Ophthalmology 2010; 94 (6):696-700.
[30] Tinelli F et al. Congenital nystagmus in two infants born from mothers exposed to methadone during pregnancy. Ital J Pediatrics. 2013, 39: 40. Published online Jul 3, 2013. doi: 10.1186/1824-7288-39-40.
[31] Mulvihill AO, Cackett PD, George ND, Fleck BW: Nystagmus secondary to drug exposure in utero. Br J Ophthalmology 2007; 91(5):613–615.

6 Regulatory Requirements and Guidance Recommendations for the Relevant Sections of the Product Labeling

A familiarity with the pertinent regulatory requirements and guidance recommendations of the prescribing information is important for understanding how the risk information may be communicated in the labeling for opioids used in maintenance treatment.

One point to keep in mind is that product labeling content does not include clinical practice guidelines, but rather, concise information to inform the safe and effective use of drugs. As such, description of best practices for management and treatment of opioid addiction during pregnancy or NOWS may be best disseminated via non-regulatory communication methods available to the FDA[32] or through publications that are developed by national organizations or professional societies.

6.1 Prescribing Information

The prescribing information is written for healthcare providers and must, among other requirements[33]:

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular, and
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

6.2 Adverse Reactions

"For the purposes of prescription drug labeling, an adverse reaction [(AR)] is an undesirable effect reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[34]

6.3 Boxed Warning

[32] See FDA Guidance: Drug Safety Information – FDA's Communication to the Public http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf
[33] See 21 CFR 201.56(a)
[34] See 21 CFR 201. 57(c)(7)

Pursuant to FDA's Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (Labeling Guidance),[35] a boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an AR so serious[36] in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling AR) that it is essential that it be considered in assessing the risks and benefits of using a drug;

- There is a serious AR that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [e.g., certain Elements to Assure Safe Use (ETASU) under Risk Evaluation and Mitigation Strategies (REMS)].[37]

Less commonly, a boxed warning can also be used in other situations:

- To highlight a warning that is especially important to the prescriber.

- For a drug that poses risk-benefit considerations that are unique among drugs in a drug class (e.g., when the drug is the only one in its class to have a particular clinically significant AR or risk and is indicated as a second line therapy because of that clinically significant AR or risk).[38]

Boxed warnings are more likely to be based on observed serious AR, but there are instances when a boxed warning based on an anticipated AR would be appropriate.[39] For example, an Embryofetal Toxicity boxed warning would be appropriate for a drug based on evidence in humans or animals that drugs in its pharmacologic class pose a serious risk of developmental toxicity during pregnancy, even though no AR was seen with the drug.

When a Boxed Warning section is warranted, it must be the first section in the full prescribing information, must be surrounded by a "box" (i.e., a single black line), and must contain a description of "contraindications or serious warnings."[40] This section must briefly explain the

[35] Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.
[36] For the purposes of prescription drug labeling, a serious AR is an AR that results in the following outcomes: Death, life-threatening AR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Furthermore, AR may be considered serious if they jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition.
[37] Labeling Guidance, p. 11.
[38] Labeling Guidance, p. 11.
[39] Labeling Guidance, p. 11.
[40] 21 CFR 201.57(c)(1).

clinically significant adverse reaction or risk and refer to more detailed information in the Contraindications or Warnings and Precautions sections.[41]

6.4 Warnings and Precautions

"This [WARNINGS AND PRECAUTIONS] section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)."[42] This section "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[43] The following factors can be used in determining if AR are clinically significant:

- The relative seriousness of the disease or condition being treated.
    - Non-serious ARs caused by drugs intended to treat minor, self-limiting conditions may be considered clinically significant.
    - However, those same ARs caused by drugs intended to treat serious or life-threatening conditions (e.g., malignancies) may be considered much less clinically significant and not appropriate for inclusion in this section.
- A high absolute risk or rate of AR occurrence
- An AR that may lead to a potentially serious outcome unless an action is taken (e.g., dosage reduction or discontinuation) to prevent a serious outcome
- An AR that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy.
- An AR that can significant affect patient compliance particularly when non-compliance has potentially serious consequences.

Each WARNINGS AND PRECAUTIONS subsection should include a succinct description of a topic and should contain the following (if known):

- A succinct description of the serious or clinically significant AR or risk
- Known risk factors for the AR
- Outcome
- Numerical estimate of the risk or AR rate
- Steps to take to prevent, mitigate, monitor, or manage the AR

[41] 21 CFR 201.57(c)(1).
[42] 21 CFR 201.57(c)(6).
[43] *See* 21 CFR 201.57(c)(6)

6.5 Contraindications

The CONTRAINDICATIONS section must describe situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal AR) clearly outweighs any possible therapeutic benefit. These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed[44].

6.6 Specific Populations

6.6.1 Pregnancy

The Pregnancy and Lactation Labeling Rule (PLLR) was finalized on December 3, 2014. The final rule removes the pregnancy categories (A, B, C, D, and X), which FDA determined were often confusing and did not accurately or consistently communicate differences in degrees of fetal risk.[45] Because risk–benefit decisions regarding use of a drug during pregnancy are more complex than the category designations suggest, reliance on the categories by health care providers may often be misplaced and could result in poorly informed clinical decision making. Instead, under the final rule, narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries are required in labeling to provide more meaningful information for clinicians. [50]

Information in the Pregnancy subsection of labeling is presented under the following subheadings:

- Pregnancy Exposure Registry (if a registry exists)
- Risk Summary
- Clinical Considerations (if applicable)
    - Disease-associated maternal and/or embryo/fetal risk
    - Dose adjustments during pregnancy and the postpartum period
    - Maternal adverse reactions
    - Fetal/neonatal adverse reactions
    - Labor or delivery
- Data

The Risk Summary provides “risk statement(s)” that describe for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug’s pharmacology. The Clinical Considerations subheading provides information to further inform prescribing and risk-benefit counseling, and may include information on risks to the pregnant woman or fetus due to the disease or condition for which the drug is indicated.

[44] See 21 CFR 201.57(c)(5)
[45] *See* Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products —Content and Format: Guidance for Industry (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

There is a common misconception that use of therapeutic products, including opioid maintenance treatment, during pregnancy is considered “off-label.” Off-label use is defined as a use of an approved product for an indication for which the product has not been approved. Pregnant women are considered a sub-population of the adult population; and therefore, are not excluded from the approved population if a product has been approved for use in adults. Therefore, use of opioid maintenance treatment in pregnant women is not considered an off-label use.

7 Discussion

The reaction of the OTP treatment system to the relabeling of Orlaam regarding risk of cardiac arrhythmia represents a real life example of the unintended consequences of communicating about risk. Additionally, patients with addictive disorders may be ambivalent or unready for treatment. Some warnings in labeling may have the consequence of discouraging patients from seeking or accepting treatment. FDA seeks the input of the Risk Communication Advisory Committee to assist us in crafting a balanced message to communicate the risk of NOWS in light of the clearly demonstrated benefits of medication assisted treatment during pregnancy.

8 Appendix: Current NOWS labeling in ER/LA opioid analgesics (approved 4/16/14)

Boxed Warning

Neonatal Opioid Withdrawal Syndrome

Prolonged use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Warnings and Precautions (5.3)*].

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TRADENAME during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

8.1 Pregnancy

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

October 7, 2013

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION[1]

National Advocates for Pregnant Women (NAPW), a 501(c)(3) non-profit advocacy and education organization that seeks to protect the rights and human dignity of all women, particularly pregnant and parenting women, respectfully submits this Citizen Petition to the Food and Drug Administration (FDA) under 21 C.F.R. § 10.30. In conjunction with medical and psychological researchers; treatment providers; reproductive health, drug policy, harm reduction, and criminal justice organizations throughout the country, NAPW requests that the Commissioner of Food and Drugs (1) refrain from implementing the FDA's neonatal opioid withdrawal syndrome (NOWS)-related labeling changes for extended-release and long-acting (ER/LA) opioid analgesics as announced on September 10, 2013, (2) present medical and scientific findings to an advisory committee to evaluate whether the proposed changes are justified, and (3) include specific language about the value of treatment for pregnant women who are opioid-dependent.

A. ACTION REQUESTED

This Citizen Petition respectfully requests that the Commissioner do the following:

1) Refrain from implementing the following FDA NOWS-related labeling changes for ER/LA opioid analgesics:
    - Boxed Warning: "For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome."
    - Full Prescribing Information: "For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts."

[1] Please note that this Citizen Petition was filed concurrently with a Petition for Stay of Action pursuant to 21 C.F.R. § 10.35.

2013-8430

FDA-2013-P-1288

- Warnings and Precautions (5.3): "For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and requires management according to protocols developed by neonatology experts."
- Patient Counseling Information: "Inform female patients of reproductive potential that chronic use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening."
- Medication Guide: "Tell your healthcare provider if you are pregnant or planning to become pregnant. Tradename may harm your unborn baby. Long-term (chronic) use during pregnancy can cause life-threatening withdrawal symptoms in your newborn baby."
- Any and all language not previously mentioned that refers to neonatal opioid withdrawal syndrome as life-threatening.

2) Remove the NOWS boxed warning.
3) Remove all references to NOWS as life-threatening, including in the patient counseling information and medication guide.
4) Modify the full prescribing information as follows to ensure that physicians who prescribe ER/LA opioid analgesics are appropriately informed about the nature and treatment of opioid dependence:
   - *(1) Opioid dependence is a chronic, relapsing medical condition with high morbidity and significant risk of death. Opioid substitution treatment (OST) with methadone or buprenorphine is the best-proven way to reduce the harms of drug use for the individual and the community, including overdose, death, and HIV infection. Persons found to be using [Tradename] without proper medical supervision or in a manner inconsistent with the prescribed dosage and/or duration should be encouraged to seek appropriate evaluation and treatment and offered assistance in doing so.*
   - *(4) Opioid dependent pregnant women should be particularly encouraged to enter treatment since OST can lessen the risk of fetal demise and dramatically improve neonatal outcome. Physicians should be aware that infants born to mothers exposed to opioids during pregnancy for either medical or nonmedical purposes may be physically dependent on opioids and may develop an abstinence syndrome shortly after birth. Generally, this syndrome is readily recognized and treated, and is not associated with adverse long-term outcomes.*
5) Replace Section 5.3 of the warnings and precautions with the following:
   - *Infants born to mothers exposed to opioids during pregnancy, for medical or nonmedical purposes, may develop an abstinence syndrome shortly after birth. This syndrome, which can present as irritability, hyperactivity and abnormal sleep patterns, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight, generally is readily recognized and treated, and is not associated with adverse long-term outcomes.*

- *Opioid dependent pregnant women should be particularly encouraged to enter OST since this can lessen the risk of fetal demise and dramatically improve neonatal outcome.*

6) Require the FDA to present its issue-specific literature reviews justifying the labeling changes to an advisory committee so that the American public can be assured that any changes made to labeling will be evidence-based.

B. STATEMENT OF GROUNDS

Petitioners do not dispute that the FDA has the authority to request safety labeling changes under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355. Neither do Petitioners dispute the potentially serious consequences of nonmedical use, misuse, or abuse of opioids, including opioid analgesics, nor the FDA's conclusion that serious outcomes are more likely to be associated with ER/LA opioid analgesics than with immediate-release opioids.

This Citizen Petition, however, challenges the FDA's NOWS-related safety labeling changes as unsupported by medical and scientific evidence. The labeling changes are false and misleading and will likely result in pregnant women being denied adequate pain treatment, discourage opioid-dependent pregnant women from seeking and being offered potentially life-saving treatment, and increase the number of pregnant women who are charged with child abuse if they do receive this treatment. Petitioners' primary concerns are the following:

1) The NOWS-related warnings are medically inaccurate and do not adhere to FDA labeling requirements.
2) FDA regulations required refusal of the NOWS-related labeling changes because the new safety information did not present a serious risk, nor were the changes based on substantial evidence or a fair evaluation of all material facts.
3) The NOWS-related warnings are inconsistent with leading national and international expert opinion on opioid use during pregnancy and other FDA regulations, and fail to consider the negative medical consequences of this labeling for maternal and fetal health.
4) The FDA's conclusion that NOWS is life-threatening is erroneous.
5) This labeling is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST.

Each of these issues is more fully addressed below.

1) The NOWS-related warnings are medically inaccurate and do not adhere to FDA labeling requirements.

The Code of Federal Regulations clearly lays out the FDA's labeling requirements for prescription drugs. 21 C.F.R. § 201 (2013). In addition to summarizing the essential scientific information that outlines the safe and effective use of the drug, the labeling must also be "informative and accurate and neither promotional in tone nor false or misleading in any particular." 21 C.F.R. § 201.56(a)(2). Moreover, "[t]he labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use

may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness." 21 C.F.R. § 201.56(a)(3).

The NOWS-related warnings stating that "[p]rolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome" are both false and misleading. Such labeling, however, could very literally be life-threatening to pregnant women and the fertilized eggs, embryos, and fetuses they carry, nurture, and sustain. There is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality. In fact, Petitioners are not aware of a single reported case of fetal demise attributed to NOWS that has been diagnosed and treated according to the well-established protocols that have been employed for decades. NOWS, when it occurs, is diagnosable, treatable, and has not been associated with long-term adverse consequences.[2]

Petitioners do not deny that NOWS is often a consequence of *in utero* exposure to opioids, including opioids prescribed for pain management and OST. Indeed, Petitioners do not endorse materials that dismiss or minimize the possibility of NOWS.[3] Nevertheless, it must also be noted that both the occurrence and severity of NOWS have been shown to be affected by a variety of factors that are unrelated to possible pharmacological effects of prenatal exposure to opiates. For example, one study demonstrated that when hospitals employed rooming in—the practice of caring for mother and newborn together in the same room immediately from birth—rather than placing them in neonatal intensive care units (NICU), newborns had less need for treatment of neonatal abstinence syndrome (NAS), shorter length of hospital stay, and significantly greater likelihood of being discharged home in the custody of their mothers.[4] Similarly, a 2010 peer-reviewed study found that only 11% of babies who boarded with their mothers required treatment of NAS compared to more than four times as many who were placed in a NICU.[5] In

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[2] *See* Walter K. Kraft & John N. van den Anker, *Pharmacological Management of the Opioid Neonatal Abstinence Syndrome*, 59;5 Pediatric Clinics of North America 1147 (2012) (concluding that "there is no evidence of long term adverse outcomes in children treated with pharmacological agents vs. infants who do not require treatment for NAS . . . ."); Stacy Seikel, *Methadone Treatment in Pregnancy . . . That Can't Be Right, Can It?*, 63;1 N.E. Fla. Med. 28, 29 (2012) (stating that research shows "minimal to no long-term negative sequelae on babies born to mothers who are on stable doses of methadone, engaged in psychosocial services, and in a stable living environment.").

[3] A 2012 pamphlet distributed by Reckitt Benckiser, manufacturer of Suboxone, misleadingly states that "[n]eonatal withdrawal *has been reported* following use of buprenorphine by the mother during pregnancy," Suboxone Pamphlet (Jan., 2012), http://www.suboxone.com/hcp/resources/documents/SF_PhysLabeling_Brochure.pdf, when in fact, in one widely-publicized study, 47% of babies whose mothers received buprenorphine under highly controlled conditions not only were "reported" to have had NOWS, but received morphine to treat the condition. Hendrée E. Jones *et al.*, *Neonatal abstinence syndrome after methadone or buprenorphine exposure*, 363;24 N. Eng. J. Med. 2320 (2010).

[4] Ronald R. Abrahams *et al.*, *An Evaluation of Rooming-In Among Substance-exposed Newborns in British Columbia*, 2010;32(9) J. Obstet. Gynaecol. Can. 866 (2010).

[5] Tolulope Saiki *et al.*, 169 Eur. J. Peds. 95 (2010).

addition, allowing mothers to breastfeed their newborns can reduce the need for NICU and medications.[6]

Evidence-based research also shows that location was associated with major differences in the treatment of NOWS. For example, " . . . to babies whose mothers received methadone [during pregnancy,] the total morphine dose administered to control neonatal abstinence syndrome averaged 4.93 mg in rural American sites, 5.04 mg in Vienna, and 34.17 mg in urban U.S. sites; the number of days of medication averaged 4.92, 9.26 and 17.91, respectively."[7]

NOWS can be evaluated and managed with scoring systems and treatment protocols that have been available for decades in standard textbooks and in numerous articles in the professional literature. Appropriate care, which may include breastfeeding and "comfort care" (e.g., swaddling and skin-to-skin contact between mother and baby), is often sufficient to prevent or minimize signs of distress in the baby. In the words of the Substance Abuse and Mental Health Services Administration (SAMHSA):

> Many times a quiet, comfortable environment is enough to provide comfort to your baby. If the symptoms are severe, your baby's doctor may prescribe medicine to help. . . . The good news is that babies born to mothers on methadone do as well as other babies; their health is much better than babies born to mothers on heroin.[8]

In spite of this research, the NOWS-related warnings draw no distinction between use and misuse of heroin or prescription opioids and opioids utilized by health care professionals in managing the pain management of pregnant women or the care of dependent pregnant women. The labeling includes numerous warnings about the consequences of NOWS, including—inaccurately—fetal demise, yet fails to provide patient counseling information explaining appropriate medical management. This is particularly problematic in a field where health care providers often lack even minimum training and where disorders associated with opiate use are highly stigmatized.[9]

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[6] Mohamed E. Abdel-Latif *et al.*, *Effects of Breast Milk on the Severity and Outcome of Neonatal Abstinence Syndrome Among Infants of Drug-Dependent Mothers*, 117;6 Pediatrics 1163 (2006).
[7] Robert Newman & Susan Gevertz, *The Complex Factors Determining Neonatal Abstinence Syndrome and Its Management*, 18 Eur. Addict. Res. 322 (2012) (citing data in a publication by A. Baewert *et al.*, 18 Eur. Addict. Res. 130 (2012)).
[8] Substance Abuse & Mental Health Services Administration, U.S. Dep't of Health & Human Services, Pub. No. [SMA] 06-4124, Methadone Treatment for Pregnant Women (2006) *available at* http://www.atforum.com/addiction-resources/documents/SAMHSAbrochurePregnantWomen2006.080904-39-5315-04-44.pdf.
[9] *See* National Center on Addiction and Substance Abuse at Columbia University, *Addiction Medicine: Closing the Gap Between Science and Practice* (2012) *available at* http://www.casacolumbia.org/upload/2012/20120626addictionmed.pdf (stating that physicians "lack the basic education and training in addiction medicine that is needed to understand the science of addiction [and] translate research evidence into practice . . . ."); White House Office of National Drug Control Policy, http://www.whitehouse.gov/ondcp/drugpolicyreform (last

Therefore, the NOWS-related labeling is false and misleading, does not comply with FDA labeling regulations, and should be changed to reflect medically accurate, informed, and sensitive treatment-focused options for pregnant women and the fertilized eggs, embryos, and fetuses they carry.

2) FDA regulations required refusal of the NOWS-related labeling changes because the new safety information did not present a serious risk, nor were the changes based on substantial evidence or a fair evaluation of all material facts.

In addition to the general labeling requirements defined in 21 C.F.R. § 201, Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act authorizes the FDA to require and, if necessary, order labeling changes if the FDA becomes aware of new safety information that it believes should be included in the labeling of a drug. 21 U.S.C. § 355(o)(4).

New safety information is defined as "information derived from clinical trial, an adverse event report, a postapproval study . . . , peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific data deemed appropriate . . . ." 21. U.S.C. § 355–1(b)(3). Other scientific data may be presented as either:

> (A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or
>
> (B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

21. U.S.C. § 355–1(b)(3)(A)–(B). The term serious risk means a risk of a "serious adverse drug experience," including death or placing the patient at immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. 21. U.S.C. § 355–1(b)(4)(A). A serious adverse drug experience may also be one that, "based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described [above]." 355–1(b)(4)(B).

Here, however, Petitioners are not aware of a single reported case of fetal demise attributed to NOWS that has been diagnosed and treated according to the well-established protocols that have been employed for decades. To the contrary, leading national and international experts have overwhelmingly concluded that proper treatment for opioid dependency can be lifesaving for the

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visited Oct. 1, 2013) (stating that "discussion of substance use disorders is too often relegated to the shadows, steeped in stigma and misunderstanding.").

pregnant woman and her future child.[10] A committee opinion by the American College of Obstetricians and Gynecologists (ACOG) states that "[n]eonatal abstinence syndrome is an expected and treatable condition that follows prenatal exposure to opioid agonists."[11] Research also shows that it has not been associated with any long-term adverse consequences.[12] Accordingly, the NOWS-related safety labeling changes are inappropriate and misleading.

Alternatively, there are also seven grounds that *require* the refusal of an application or supplemental application, including relabeling, in 21 U.S.C. § 355(d)(2013). Petitioners focus on (5) and (7), but emphasize that any one of the seven grounds, on its own, would require refusal.

21 U.S.C. § 355(d)(5) explains that the refusal is required if, " . . . there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." Substantial evidence is defined as:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(e). Here, there is not simply a lack of "substantial evidence" showing that NOWS is life-threatening; there is no evidence whatsoever. To reiterate: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience" shows that NOWS is diagnosable and treatable, and has not been associated with any long-term adverse consequences.

Another ground that requires refusal is if, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." 21 U.S.C. § 355(d)(7). Here, the NOWS boxed warning is indisputably false and misleading. Indeed, leading national and international experts have overwhelmingly concluded that proper treatment for opioid dependency can be lifesaving for the pregnant woman and her future child.

Therefore, even if the FDA had the ability to approve safety labeling changes under 21 U.S.C. 355(o)(4), the evidentiary threshold for doing so conflicts with the strict standards in 21 U.S.C. § 355(d). As they currently stand, FDA regulations for labeling and relabeling vary dramatically, and as such, the FDA should have issued an order refusing to approve the NOWS-related warnings of the relabeling application.

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[10] The American College of Obstetricians and Gynecologists, *Opioid Abuse, Dependence, and Addiction in Pregnancy*, Committee Opinion No. 524 (May 2012) *available at* http://www.acog.org/~/media/Committee%20Opinions/Committee%20on%20Health%20Care%20for%20Underserved%20Women/co524.pdf?dmc=1&ts=20130723T0355371185.

[11] *Id.*

[12] *See* Kraft, Seikel, *supra* note 2.

3) The NOWS-related warnings are inconsistent with leading national and international expert opinion on opioid use during pregnancy and other FDA regulations, and fail to consider the negative consequences of this labeling for maternal and fetal health.

By inaccurately focusing on NOWS, the FDA's warnings fail to recognize that abrupt discontinuation and/or wide swings in concentration levels of opioids during pregnancy may cause fetal distress and pregnancy loss.[13] Leading national and international experts urge pregnant women to seek treatment in lieu of stopping opioid intake altogether.

A SAMHSA brochure directed at opioid-dependent pregnant women states:

> If you're pregnant and using drugs such as heroin or abusing opioid prescription pain killers, it's important that you get help for yourself and your unborn baby. Methadone maintenance treatment can help you stop using those drugs. It is safe for the baby, keeps you free of withdrawal, and gives you a chance to take care of yourself. . . . *MMT can save your baby's life.*[14]

Discontinuation of opiate substitution treatment during pregnancy is likely to result in relapse to nonmedical use of opioids, including IV heroin, which substantially increases risk to both the expectant mothers and their babies.[15] The efficacy and safety of OST have been well documented in many countries over many years and OST is strongly endorsed by the World Health Organization, United Nations Office on Drugs and Crime, and the Joint United Nations Programme on HIV/AIDS. In March, 2013, a United Nations report condemned addiction treatment policies or lack thereof in some parts of the world as "tantamount to torture or cruel, inhuman or degrading treatment."[16] The report stated that a "particular form of ill-treatment and possibly torture of drug users is the denial of opiate substitution treatment," and it is considered a human rights violation when it occurs in jails and prisons.[17]

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[13] The American College of Obstetricians and Gynecologists, *Nonmedical Use of Prescription Drugs*, Committee Opinion No. 538 (Oct. 2012) *available at* http://www.acog.org/~/media/Committee%20Opinions/Committee%20on%20Health%20Care%20for%20Underserved%20Women/co524.pdf?dmc=1&ts=20130723T0355371185.

[14] *See* SAMHSA *supra* note 8 (emphasis added).

[15] World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* (2009) *available at* http://whqlibdoc.who.int/publications/2009/9789241547543_eng.pdf.

[16] U.N. Human Rights Council, *Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment*, U.N. Doc. A/HRC/22/53 (Feb. 1, 2013) (by Juan E. Méndez) *available at* http://www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf.

[17] *Id.*

The World Health Organization states:

> For women who are pregnant or breastfeeding, opioid agonist maintenance with methadone is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on antenatal care and parenting of young children. Opioid-dependent women not in treatment should be encouraged to start opioid agonist maintenance treatment with methadone or buprenorphine. Pregnant women who are taking opioid agonist maintenance treatment should be encouraged not to cease it while they are pregnant. Although many women want to cease using opioids when they find out they are pregnant, opioid withdrawal is a high-risk option because a relapse to heroin use will affect the capacity to care for the child. In addition, severe opioid withdrawal symptoms may induce a spontaneous abortion in the first trimester of pregnancy, or premature labour in the third trimester.[18]

Medical research indisputably shows that the critical problem is not NOWS, but maternal dependence on opioids that goes untreated. As already stated throughout this Citizen Petition, proper treatment for opioid dependent pregnant women is not only appropriate, but also can be life-saving. Indeed, the FDA itself recognizes the special role that methadone can play in protecting the health and well-being of the opioid-dependent pregnant woman and her expectant child. For instance, the FDA's federal opioid treatment standards require that there be "... a preference for pregnant women in admitting patients to interim maintenance [when a position is not immediately available in a "comprehensive" OTP] and in transferring from interim maintenance to comprehensive maintenance treatment." 42 CFR § 8.12(j)(1). Another regulation carves out a "treatment admission exception" for pregnant patients. 42 CFR § 8.12(e)(3). Clearly, the FDA promulgated these regulations prioritizing treatment for pregnant women because it understands the grave risks associated with the abrupt discontinuation of opioids and their continued misuse or abuse, and the protective role that can be played by OST.

Moreover, even for women who are not opioid-dependent, "there are very few options for the treatment of severe chronic pain during pregnancy, and opioid analgesics have been relied upon as the safest alternative in conditions requiring treatment for pain."[19] Obviously, pain does not disappear when a woman becomes pregnant, and women during pregnancy can and do experience pain from a variety of causes, but nevertheless, the NOWS-related warnings will likely result in pregnant women being denied adequate pain treatment.

> This would not only be inhumane, but we also do not clearly know the impact of untreated pain during pregnancy. Untreated pain would certainly present a major stressor for the pregnant woman and her fetus, with potential adverse effects. This concern applies not only to pain throughout pregnancy but also pain during labor and delivery,

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[18] World Health Organization, *supra* note 11.

[19] Letter from Massachusetts Society for Addiction Medicine to Martha Coakley, Massachusetts Attorney General, (June 6, 2013) *available at* http://masam.org/yahoo_site_admin/assets/docs/Coakley_letter_BlackBox_State_AG_FDA_response.156114529.pdf.

where judicious use of narcotic medications is often necessary, and for which safe administration protocols have been developed by obstetricians and anesthesiologists.[20]

Unfortunately, the FDA's NOWS-related warnings, contrary to all relevant evidence, seem intended to discourage pregnant women from seeking appropriate pain treatment or appropriate and potentially life-saving treatment for dependence.

4) The FDA's conclusion that NOWS is life-threatening is erroneous.

In its letter to application holders for ER/LA opioid analgesics, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(o)(4)), the FDA states:

> FDA has also become aware of the increasing frequency of neonatal abstinence syndrome (NAS), a term which includes neonatal opioid withdrawal syndrome (NOWS), as well as neonatal withdrawal from other drugs. An assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001). The same study documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001]). . . . FDA has determined that these study findings, in addition to the data and information discussed above, demonstrate the continuing trends of serious risks related to the use of opioid analgesics, and the need for modifications to product labeling to more effectively communicate the serious risks associated with ER/LA opioid analgesic use overall, and during pregnancy, and to more clearly describe the population in whom these drugs should be used, in light of these serious risks.[21]

Neither this paragraph, nor the sole study to which it refers, states that NOWS is life-threatening. The only reference cited did not even study morbidity or mortality of either mothers or their offspring, but rather, describes incidence during four separate years of NOWS and of "mothers diagnosed with antepartum opiate use."[22] The study presented data from two obviously very different databases because during the years in question, data was analyzed for 9,674 babies with NAS, but for just 4,563 mothers with reported opiate use during pregnancy.[23] Furthermore, the study made absolutely no distinction between prescribed use and misuse or abuse of drugs, nor whether used illicitly or taken as prescribed for management of dependence or pain. Nor was there any reference to whether fetal exposure occurred over the course of days, weeks, or months

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[20] *Id.*

[21] Letter from FDA to ER/LA opioid analgesic application holders (Sept. 10, 2013) *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf.

[22] Stephen Patrick *et al.*, *Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009* 307;18 JAMA 1934 (2012).

[23] *Id.*

prior to delivery. With respect to methadone in particular, data was lumped together with all other opiates, without regard to whether it was taken as part of a prescribed treatment regimen and, if so, whether given for management of pain or for dependence. By relying on this single study—one that does not even address fatality—the FDA has failed to acknowledge the extensive worldwide literature on the subject.

Petitioners are aware that there are reports claiming to identify major adverse effects, beyond merely the occurrence of NOWS, on the neonate as a result of *in utero* exposure to opioids. For example, a 2009 publication reported on a retrospective study of 450 babies whose mothers had received methadone treatment for opioid dependence during pregnancy.[24] The authors concluded that these infants " . . . are extremely vulnerable and draw heavily on healthcare resources."[25] Like many others in this field, however, this study was flawed. It failed to consider that the amount of methadone being given to the pregnant women was significantly below recommended doses and neglected to take into account the duration of the treatment given. The "median daily prescribed dose of methadone" was 50 mg, which is well below what is recognized as being associated with optimal outcomes (60 – 100 mg per day for most patients, with higher doses generally required during pregnancy).[26] Also, the mothers could have been receiving OST throughout their pregnancy or for only a few days before delivery.[27]

Another study in 2002 specifically analyzed the "relationship between maternal methadone [maintenance] dosage and neonatal withdrawal," and concluded that "[m]aternal methadone dosage was associated [directly] with duration of neonatal hospitalization, neonatal abstinence score, and treatment for withdrawal."[28] In this case, the median dose of methadone during gestation was 20 mg, which is substantially less than what is recognized as being associated with optimal outcomes.[29]

Therefore, while Petitioners acknowledge that there is conflicting data on the prevalence of NOWS and some research suggesting some health consequences or influences following proper treatment, there still remains no study specifically claiming that NOWS is life-threatening.

5) This labeling is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST.

The FDA's relabeling will occur in a real life context in which health care providers and child welfare workers who are poorly trained in addiction treatment are likely to use the NOWS-related warnings to justify punitive and counterproductive child welfare interventions against pregnant women and new parents. This concern is not hypothetical. Today, even without the

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[24] C. Dryden *et al.*, *Maternal methadone use and the consequences on baby*, 116 BJOG 665 (2009).
[25] *Id.*
[26] *Id.*
[27] *Id.*
[28] J.S. Dashe *et al.*, *Relationship between maternal methadone dosage and neonatal* withdrawal, 100 Obstet. Gynecol. 1244 (2002).
[29] *Id.*

false and misleading NOWS-related warnings challenged in this Citizen Petition, misinformation about and prejudice against OST have resulted in punitive child welfare actions taken against pregnant women and parents because they receive such treatment.

While this specific misuse of the child welfare system has not been subject to systematic study, and despite the fact that child welfare proceedings are generally confidential and do not come to public attention, NAPW has identified numerous cases in which state authorities have sought to punish pregnant women because they obtained medically approved methadone treatment. Over the past several years, NAPW has also received numerous requests for help from methadone treatment providers reporting punitive child welfare interventions.

For example, a staff member at a Michigan methadone maintenance facility wrote to NAPW seeking help because women participating in methadone maintenance treatment (MMT) were being placed on the abuse and neglect registry by local child protective services "for the sole reason of being on methadone maintenance during pregnancy." The staff member explained:

> Our local hospitals, court system, and Child Protective Services are opening cases on any woman whose child experiences neonatal abstinence syndrome after birth. The fact that the woman was legitimately participating in MMT and under a doctor's care is irrelevant to these agencies. . . . It is infuriating that none of these professionals are open to reviewing the facts about treatment and would instead criminalize women who have done nothing but make the right choice to participate in treatment for the sake of their child. CPS is also informing women that they are not allowed to breast feed while on methadone, unless they are tapering out of the program. If they continue to breast feed without tapering, they will be taken to court. The fact that all research and medical findings support breastfeeding while on methadone is being ignored. The uninformed actions of CPS are preventing women from seeking a potentially life saving treatment. We have heard of many women who have opted to continue illicit drug use rather than get the help that they need because of the actions of CPS. They are not telling their physician that they use drugs, and are discharged from the hospital before withdrawals set in. This means that babies are going through withdrawal at home, without needed medical attention. . . . I work with some amazing women who have made great strides in their recovery. The discrimination and harassment they are currently going through breaks my heart.[30]

NAPW has received similar requests for help from methadone treatment providers in Tennessee and Georgia. The administrator of a new methadone treatment program in Georgia wrote: "I have 5 patients with varying degrees of problems with the DHR Division of Child and Family Services. Most of our patients are unable to hire private attorneys to fight for their children. The problem is one of ignorance, prejudice and misinformation about addiction as an illness and recovery as a process."[31] One of the examples provided:

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[30] Email from P.S. to NAPW (May 22, 2012) (on file with NAPW).
[31] Email from R.R. to NAPW (July 3, 2005) (on file with NAPW).

> A new mother whose baby showed signs of withdrawal (which is typical, babies born to methadone patients may be physically dependent at birth and must be treated for withdrawal) in the hospital has lost custody to a foster family with "special training" to manage its treatment. This mother was compliant with treatment and not using illicit drugs. This case went in front of a juvenile judge.[32]

In Tennessee, in just the past four months, two women contacted NAPW because judges overseeing child welfare cases demanded that mothers "detox from methadone" if they wanted to maintain or regain custody of their children. In both cases, the mothers were receiving therapeutic MMT as prescribed by their physicians.[33]

In California, the Department of Children and Family Services removed newborn twins from their mother because she had received methadone treatment during pregnancy and the babies had displayed signs of NAS at birth. *In re C.R. v. R.H.*, 2012 WL 4049010, at *1 (Cal. Ct. App. 2d. Sept. 14, 2012). The juvenile court found that there was substantial evidence of a risk of harm to the children because "they suffered physical harm as a direct result of mother's drug abuse issues." *Id.* at *4. On appeal, the mother's obstetrician testified on her behalf, explaining that:

> [The twins] would not have experienced those symptoms if mother had been allowed to breast feed them as planned. The obstetrician also opined that mother's methadone levels were appropriate, and that reducing or stopping methadone during pregnancy could have caused the twins to suffer withdrawal symptoms in utero serious enough to cause a loss of the pregnancy.

Id. at *3. Nevertheless, the appellate court upheld the juvenile court's decision to separate the babies from their mother permanently.

In one of the many cases in which NAPW participated, a new mother in Connecticut who had been enrolled in methadone treatment while pregnant was charged with child abuse and neglect under the state's civil child welfare law. *In re R.C.*, No. T11-CP04-011978-A (Conn. Super. Ct. 2005). This mother had received regular prenatal care, provided her physicians with complete and honest information regarding her medical history, and attempted to comply with all requests by both her methadone treatment program and the hospital staff after delivery. Staff at the hospital, however, were so inadequately trained and unfamiliar with methadone treatment that they viewed it as no different from active addiction and contacted the Department of Children and Families. The Department, in turn, drew on the same erroneous conclusion and charged the new mother with child abuse and neglect.

In another case discussed in a 2012 article, a family court judge told a mother that he would not close her child welfare case until she "got off methadone."[34] When she introduced letters from

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[32] *Id.*

[33] Email from A.F. to NAPW (Aug. 8, 2013) (on file with NAPW); Email from R.N. to NAPW (Sept. 27, 2013) (on file with NAPW).

[34] Rachel Blustain, *Medical Consensus or Child Abuse? Moms on Methadone Caught in the Middle*, The Daily Beast (Sept. 2, 2012),

experts testifying that the federal government recommends methadone maintenance for opiate-addicted women, she said the judge ignored the medical evidence, telling her, "I can make an airplane out of these papers and glide it across the courtroom."[35]

New Jersey provides a particularly clear example of state action taken against pregnant women who have received methadone treatment. For example, in *N.J. Div. of Youth & Family Servs. v. E.P.A.*, No. A-6169-05, slip op. at 13 (App. Div. Oct. 15, 2007), a mother was charged with parental neglect because her son tested positive for methadone at birth. The court received a letter from her treatment center confirming that she "had refrained from drug use, except methadone, for seventeen months," clarifying that she had not used any illegal drugs in the six months before she became pregnant and throughout her entire pregnancy. Nevertheless, the court characterized the receipt of prescribed methadone as "an inability to eliminate a reliance on methadone, itself an addictive drug," and upheld the lower court's order terminating the mother's parental rights.

A court in a similar case likened drug treatment to heroin use, finding neglect because "a woman using heroin *or on methadone maintenance* should find out about the risks to a child before becoming pregnant and opt to avoid that harm if the risks are great." *N.J. Div. of Youth & Family Servs. v. E.C.*, No. A-4219-06, slip op. at 12 (App. Div. Apr. 28, 2008) (emphasis added). The court found harm because the NAS the child allegedly experienced arose "[a]s a consequence of E.C.'s need for methadone, prescribed or otherwise." *Id.* at 19.

In *N.J. Div. of Youth & Family Servs. v. A.J.*, No. FN 07-346-10 (Law Div. Feb. 22, 2011), a woman who took prescribed methadone throughout her pregnancy as directed by her physician was reported for child abuse and neglect because the infant presented with NAS at birth. In the only case NAPW could find in which there was any evidence presented by scientific experts regarding addiction and methadone treatment during pregnancy, the trial court held that the Division of Child Protection and Permanency had failed to meet its burden to prove that a child was abused and neglected. This decision, which held that "the evidence supports a finding that his diagnosis, at birth, of Neonate Addiction Syndrome [sic] is an outcome that is consistent with the medical standard of care for opioid addicted pregnant women," was never published. Slip Op. at 32.

Most recently, however, a New Jersey appellate court in *N.J. Div. of Youth & Family Servs. v. Y.N.*, A-5880-11T2, 66 A.3d 237 (App. Div. 2013), upheld a lower court ruling that a newborn was abused and neglected because, after birth, he experienced NAS. The child's mother, while pregnant, obtained federally recommended, medically approved, and supervised methadone treatment from a methadone treatment program. She sought treatment to help her address an addiction to prescription Percocet, and her doctor advised her that abrupt withdrawal from Percocet could risk harm to the fetus, potentially causing her to lose the pregnancy altogether. Her treatment was successful and she was able to abstain from the use of illegal drugs during her pregnancy.

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http://www.thedailybeast.com/articles/2012/09/02/medical-consensus-or-child-abuse-moms-on-methadone-caught-in-the-middle.html.

[35] *Id.*

The baby was born healthy, full term, with Apgar scores of 8 and 9.5. Shortly after birth, the baby showed the predicted signs of NAS, for which he was successfully treated, and was released from the NICU to his mother. In spite of this success story, the mother was reported to the Division of Youth and Family Services, which subsequently charged her with abuse and neglect. The trial court found that the child suffered harm due to a positive drug screen for methadone and a diagnosis of NAS. The New Jersey Court of Appeals upheld this ruling, concluding that the expected and treatable side effects of methadone treatment obtained by a pregnant woman may be treated as "harm" for purposes of the state's abuse and neglect statute. N.J.S.A. 9:6-8.21(c)(4).

The effect of this ruling, if not overturned by the New Jersey Supreme Court, will be a judicially created penalty on pregnant women who obtain methadone treatment: obtain such treatment and lose your constitutional right to parent that child once born. The mother is currently seeking review by the state supreme court. She is supported by more than four dozen national and international experts and organizations in an amicus (friend of the court) brief.[36]

NAPW has also identified or been contacted about numerous other cases in Alabama, Florida, Kentucky, Michigan, New York, Pennsylvania, South Carolina, and Texas, where pregnant women and parents have been threatened with loss of custody of their children or have actually lost custody of their children because they have been receiving some form of OST.

These cases have occurred even without the FDA's labeling changes. The NOWS-related warnings will undoubtedly increase the likelihood of such cases that endanger the health of pregnant women and new mothers by creating penalties for the receipt of OST.

In addition, failure of the FDA to draw any distinction between the use or misuse of opioids and compliance with a prescribed, strongly endorsed, evidence-based therapeutic regimen will also discourage women who need help from seeking it. This failure, not NOWS, is what could truly prove life-threatening for pregnant women and their babies.

Conclusion

For the foregoing reasons, there is no rational connection between the available research on NOWS and the FDA's NOWS-related warnings. The labeling changes are totally lacking in scientific support and the professional views of experts in the field. Indeed, the FDA's decision is so implausible that it cannot be ascribed to a difference in view or the product of agency expertise. It will prove harmful to many pregnant women and their babies, and surely will result in the death of some. It will also severely impact the credibility of this agency, which plays such a crucial role in safeguarding the healthcare of the American public.

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[36] Brief of *Amici Curaie* in Support of Defendant-Petitioner's Petition for Certification, *N.J. Div. of Youth & Family Servs. v. Y.N.*, A-5880-11T2, 66 A.3d 237 (App. Div. 2013) (Aug. 1, 2013), *available at* http://www.advocatesforpregnantwomen.org/main/publications/brief_bank/.

C. ENVIRONMENTAL IMPACT

According to 21 C.F.R. 25.31, this Citizen Petition qualifies for a categorical exclusion from the requirement for the submission of an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of this Citizen Petition.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and includes representative data and information known to the Petitioners that are unfavorable to the Citizen Petition.

Respectfully submitted,

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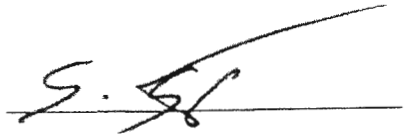

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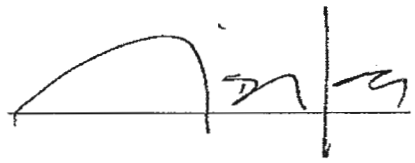

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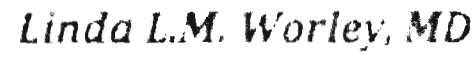

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APR 1 6 2014

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RE: Docket Nos. FDA-2013-P-1288 and FDA-2013-P-1289

Dear Petitioner:

This letter responds to your citizen petition, docket number FDA-2013-P-1288 (Citizen Petition), and petition for stay of action, docket number FDA-2013-P-1289 (Petition for Stay), both dated October 7, 2013 (collectively, Petitions). The Petitions collectively request that the Food and Drug Administration (FDA or Agency): (1) stay indefinitely the implementation of (*i.e.*, refrain from implementing), its neonatal opioid withdrawal syndrome (NOWS)-related safety labeling changes (SLCs) for extended-release/long-acting (ER/LA) opioid analgesics (Citizen Petition at 1-2; Petition for Stay at 1-2); (2) "remove the NOWS boxed warning" from ER/LA opioid analgesic labeling (Citizen Petition at 2); (3) "remove all references [in ER/LA opioid analgesic labeling] to NOWS as life-threatening, including in the patient counseling information and medication guide" (Citizen Petition at 2); and (4) present its NOWS-related issue-specific literature reviews to an Advisory Committee (Citizen Petition at 2). The Petitions further request that FDA: (1) include Petitioner-provided language regarding opioid substitution treatment (OST) in the full prescribing information of ER/LA opioid analgesic labeling (Citizen Petition at 2); and (2) replace section 5.3 of the Warnings and Precautions section of ER/LA opioid analgesic labeling with certain Petitioner-provided language (Citizen Petition at 2).

We have considered the Petitions carefully. For the reasons that follow, your requests are denied.

I. BACKGROUND

A. NOWS

NOWS is a constellation of signs and symptoms exhibited by neonates[1] born to women who have used or abused opioid drugs during pregnancy. Usually within the first 72 hours of life, infants with NOWS exhibit irritability with a high pitched cry, hyperactive primitive reflexes, hypertonicity, tremors, feeding difficulties, gastrointestinal disturbances and failure to thrive.[2,3]

[1] The term "neonate" generally refers to newborn infants up to 28 days old. For the purpose of this response, the term neonate, newborn, "baby," and infant will be used interchangeably.

[2] Jansson L and Valez M. Neonatal abstinence syndrome. *Curr Opin Pediatr* 2012; 24:252-258.

[3] Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31.

Severity of symptoms is typically determined by applying an assessment tool such as the Finnegan scoring system[4] or a modified version thereof. The infant is evaluated over time and if the score reaches a pre-specified cut-off point, the infant is considered to have severe symptoms.[5] Depending on symptom severity, treatment may range from comfort care (*e.g.*, swaddling, non-nutritive sucking) to administration of opioid-containing medications.[6] Further discussion of this condition occurs in section II, below.

B. NOWS Safety Labeling Changes for ER/LA Opioid Analgesics

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[7] authorizes FDA to require holders of approved drug applications to make SLCs if the Agency becomes aware of new safety information that FDA determines should be included in the labeling of the drug. *New safety information* is defined in part as:

> Information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the [Agency] about, among other things, a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was approved, or since the last assessment of the approved REMS.[8]

On September 10, 2013, FDA notified application holders for ER/LA opioid analgesics that, pursuant to section 505(o)(4) of the FD&C Act, safety labeling changes were needed for ER/LA opioid analgesics.[9,10] FDA explained its rationale, and the new safety information upon which it relied in exercising this authority.[11] The Agency intended these changes to more effectively communicate the serious risks of misuse, abuse, NOWS, addiction, overdose, and death associated with the use of ER/LA opioid analgesics.

The NOWS-related changes were based on new safety information derived primarily from a cross-sectional study by Stephen W. Patrick published in 2012 in the *Journal of the American*

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[4] *See* Finnegan LP, Connaughton JF, Jr., Kron RE, *et al.*, Neonatal abstinence syndrome: assessment and management. *Addictive diseases* 1975; 2:141-158.

[5] *See* Jansson L and Valez M. Neonatal abstinence syndrome. *Curr Opin Pediatr* 2012; 24:252-258.

[6] *Id.*

[7] 21 U.S.C 355(o)(4). *See also* Guidance for Industry: *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013) ("SLC Guidance").

[8] *See* section 505-1(b)(3) of the FD&C Act.

[9] Pursuant to section 505(o)(4) of the FD&C Act, FDA notified holders of approved NDAs and holders of approved ANDAs without a currently marketed reference listed drug approved under a NDA.

[10] *See* Letter to Application Holders: Labeling Supplement and PMR Required (SLC/PMR Letter), available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf.

[11] *See* SLC/PMR Letter at 1-2, describing certain safety labeling changes and post-marketing requirements (PMRs).

Medical Association (JAMA) (the "Patrick study").[12] As the Agency explained on page 2 of the SLC/PMR Letter:

> FDA has also become aware of the increasing frequency of neonatal abstinence syndrome (NAS), a term which includes [NOWS], as well as neonatal withdrawal from other drugs. An assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001).[13] The same study documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001]).[14]

The Agency determined that the above analysis, when taken together with other information and analyses, constituted new safety information about NOWS that should be included in the labeling for all ER/LA opioid analgesics.

The NOWS labeling set forth in the SLC/PMR Letter raised the prominence of the NOWS warning and better emphasized the need for providers to be prepared for NOWS. On April 7, 2014, FDA concluded the discussion period with the ER/LA opioid analgesic sponsors and approved NOWS labeling changes.[15] The final labeling is identical to the NOWS labeling set forth in the SLC/PMR Letter, except for the following changes (deletions in strikethrough and additions in bold). The changes clarify, among other things, that NOWS is potentially life-threatening **if not recognized and treated**:

- In the boxed warning in Highlights: "~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged use **of TRADENAME** during pregnancy can result in ~~life-threatening~~ neonatal opioid withdrawal syndrome**, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.X~~3~~).**"
- In the boxed warning: "Neonatal Opioid Withdrawal Syndrome: ~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged ~~maternal~~ use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening **if not recognized and treated,** and requires management according to protocols developed by neonatology experts**. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available** *[see Warnings and Precautions (5.X~~3~~)]*."

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[12] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307(18):1934-30.

[13] *Id.*

[14] *Id.*

[15] *See* 505(o)(4)(D) and SLC Guidance at 9.

- In the Warnings and Precautions section: "5.X~~3~~ Neonatal Opioid Withdrawal Syndrome: ~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged ~~maternal~~ use of TRADENAME during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening **if not recognized and treated,** and requires management according to protocols developed by neonatology experts. **If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**

  Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn."

- In section 8, Special Populations: "8.1 Pregnancy: **Clinical Considerations: Fetal/neonatal adverse reactions:** Prolonged use of opioid analgesics during pregnancy ~~may cause~~ **for medical or nonmedical purposes can result in physical dependence in the neonate and** neonatal opioid withdrawal syndrome **shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly** *[see Warnings and Precautions (5.X~~3~~)]*."

- In section 17, Patient Counseling Information: "Neonatal Opioid Withdrawal Syndrome: Inform female patients of reproductive potential that ~~chronic~~ **prolonged** use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening **if not recognized and treated** *[see Warnings and Precautions (5.X~~3~~)]*."

- In the Medication Guide, "Tell your healthcare provider if you are: pregnant or planning to become pregnant. ~~TRADENAME may harm your unborn baby. Long-term (chronic)~~ **Prolonged** use **of TRADENAME** during pregnancy can cause ~~life-threatening~~ withdrawal symptoms in your newborn baby **that could be life-threatening if not recognized and treated**."

II. DISCUSSION

The Petitions request that FDA stay the implementation of (*i.e.*, decline to implement) the NOWS labeling set forth in the SLC/PMR Letter. The Petitions also request that FDA eliminate, or stay implementation of, any references to NOWS as "life-threatening" in ER/LA opioid analgesic labeling. In addition, the Petitions request that FDA include several statements related to OST in the ER/LA opioid analgesic labeling, and that FDA provide its NOWS-related scientific assessments to an advisory committee for review. For the reasons described below, these requests are denied.

A. NOWS is Life-threatening if Not Recognized and Treated

The Petitions assert that NOWS is not life-threatening, and that the NOWS labeling described in the SLC/PMR letter is medically inaccurate and inconsistent with expert guidelines (Citizen Petition at 3-6 and 10-11; Petition for Stay at 2-5 and 9-11).[16] Specifically, the Petitions assert that "[t]here is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality," and that "NOWS, when it occurs, is diagnosable, treatable, and has not been associated with long-term adverse consequences (Citizen Petition at 4; Petition for Stay at 3). The Petitions request that FDA substitute the following language in Section 5.3 of the warnings and precautions section:

> Infants born to mothers exposed to opioids during pregnancy, for medical or nonmedical purposes, may develop an abstinence syndrome shortly after birth. This syndrome, which can present as irritability, hyperactivity and abnormal sleep patterns, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight, generally is readily recognized and treated, and is not associated with adverse long-term outcomes. (Petition at 2).

FDA agrees that NOWS is diagnosable and treatable. However, NOWS can be life-threatening if it goes unrecognized and therefore untreated.[17] If a mother has not been identified as an opioid user, the infant may not be monitored for the emergence of withdrawal symptoms. Similarly, if the mother requires use of an opioid for an extended period during pregnancy, but this has not been taken into consideration for impact on the newborn, the infant may not be monitored for the emergence of withdrawal symptoms. If an infant develops NOWS and doctors do not recognize it, or are not anticipating it, there could be problems with diagnosis or a delay in therapy. Failure to treat NOWS, in turn, could result in unnecessary distress in, and even threaten the lives of, infants who were exposed to opioids in utero. The American Academy of Pediatrics, in its clinical report on neonatal drug withdrawal, states that "withdrawal from opioids or sedative-hypnotic drugs may be life-threatening."[18] Other recent studies reflect the same view. For example, Jones, *et al.*, describe the characteristics of neonatal abstinence syndrome (NAS) — a term that includes withdrawal from opioids — by saying, "When left untreated NAS can result in serious illness (*e.g.* diarrhea, feeding difficulties, weight loss and seizures) and death."[19]

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[16] FDA also received comments to both dockets expressing concern regarding the characterization of NOWS as "life-threatening." *See* FDA-2012-P-1288-0004, FDA-2012-P-1289-0004 (both from the American College of Obstetricians and Gynecologists, attaching the American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012, and asserting that NOWS is "without subsequent pathophysiology").

[17] NOWS has been described as potentially "life-threatening" in some ER/LA opioid labeling since at least 2012. *See, e.g.*, Avinza (morphine sulfate) extended-release capsules Labeling, NDA 021260, approved 7/9/12 (Section 8.6: Neonatal Opioid Withdrawal Syndrome: ". . . Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts."), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021260s015lbl.pdf.

[18] American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560. This study does, however, acknowledge that "ultimately, drug withdrawal is a self-limited process."

[19] Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31. In support of this assertion, the authors cite a chapter by LP Finnegan in the second edition of Primary Pediatric Care, edited by RA Hoekelman, SE Friedman, NM Nelson, *et al.* *See id.*

The NOWS labeling changes approved on April 14, 2014 explicitly state that NOWS is potentially life-threatening **if not recognized and treated**. The Agency believes that these clarifying changes more precisely articulate the risks of NOWS. FDA also included this clarifying language to avoid any implication that ER/LA opioid analgesics should never be used during pregnancy due to the risk of NOWS. The Agency agrees that opioid therapy may be necessary for the health and well-being of a pregnant woman. It does not intend to discourage the medically appropriate use of opioids in pregnant women. [20]

FDA disagrees with the Petitions' assertions (and proposed labeling statement) that NOWS "is not associated with adverse long-term outcomes." Although data regarding long-term risks of NOWS are limited, and more research is needed, there are suggestions in published literature that NOWS may be associated with substantive long-term effects on neurologic and cognitive functioning.[21] Thus, at present, FDA has not determined that NOWS "is not associated with adverse long-term outcomes." [22]

B. Legal and Regulatory Requirements

1. Section 505(o)(4) of the FD&C Act

Pursuant to section 505(o)(4)(A) of the FD&C Act, "[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person." The Petitions and a comment to both dockets[23] challenge both the notion of NOWS as a "serious risk," and the propriety of FDA's reliance on a study by Patrick, *et al.*,[24] as the source of "new safety information . . . about a serious risk"[25] that forms the basis for the NOWS-related labeling changes. For the reasons described below, FDA disagrees.

A "serious risk" is a "risk of a serious adverse drug experience,"[26] which is defined as an adverse drug experience that:

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[20] For example, the boxed warning, and warnings and precautions sections state, "**If opioid use is required** for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available" (emphasis added).

[21] *See, e.g.*, Rosen TS and Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age *The Journal of Pediatrics* 1982; 101(2):192-196; Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders *Toxicology Letters* 2003; 140-141:171-181; Wahlsten VS and Sarman I. Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatrica* May 2013; 102(5):544-9.

[22] The Agency also notes that a risk does not need to be associated with "long-term" consequences to be included in drug labeling.

[23] FDA-2013-P-1288-0006, FDA-2012-P-1289-0005 (same comment).

[24] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307 (18): 1934-30.

[25] Section 505-1(b)(3)(A) of the FD&C Act (defining *new safety information*).

[26] Section 505-1(b)(5) of the FD&C Act.

(A) Results in:
1. Death;
2. An adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly or birth defect; or

(B) Based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).[27]

As stated above, NOWS may result in, among other things, diarrhea, feeding difficulties, weight loss, and seizures.[28] It thus can result in a prolongation of existing hospitalization, particularly in infants with severe symptoms who need opioid therapy.[29] Moreover, NOWS may require a medical intervention (*e.g.*, opioid treatment) to prevent inpatient hospitalization or prolongation of existing hospitalization.[30] NOWS therefore constitutes a "serious" risk as defined by statute, and thus is a valid subject for safety labeling changes under section 505(o)(4).[31]

Further, information derived from the Patrick study suggests an increasing incidence of NOWS,[32] and that the labeling of ER/LA opioids should emphasize NOWS risks and adding additional NOWS warnings. In particular, the Patrick study showed an increasing prevalence of opioid use during pregnancy and a concomitant increase in the rate of cases of NAS, including cases of NAS from opioids (*i.e.*, NOWS).[33] (The Patrick study also found that infants with NAS were significantly more likely to have respiratory diagnoses (30.9% of newborns with NAS vs.

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[27] Section 505-1(b)(4) of the FD&C Act.

[28] *See, e.g.*, Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31.

[29] *See* American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560.

[30] *See id.*

[31] Notably, although the "Warnings and Precautions" section requires the inclusion of "clinically significant" adverse reactions, such adverse reactions do not need to rise to the level of being "serious" to be included in the labeling. *See* 21 CFR 201.57(c)(6).

[32] Additional studies, though not relied upon as new safety information, also support this conclusion. *See* Creanga, AA, Sabel, JC, Ko, JY, Wasserman, CR, Shapiro-Mendoza, CK, Taylor, P, *et al.* (2012). Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstetrics and gynecology,* 119; 924-933; Kelly, L, Dooley, J, Cromarty, H, Minty, B, Morgan, A, Madden, S, *et al.* (2011). Narcotic-exposed neonates in a First Nations population in northwestern Ontario: incidence and implications. *Canadian family physician Medecin de famille canadien,* 57; e441-e447; Kellogg, A, Rose, CH, Harms, RH, & Watson, WJ (2011). Current trends in narcotic use in pregnancy and neonatal outcomes. *American journal of obstetrics and gynecology,* 204; 259-4.

[33] *See* n. 11 and 12, *supra.* Specifically, FDA found that this "assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001). [The Patrick study also] documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001])." SLC/PMR Letter at 3.

8.9% without NAS), feeding difficulty (18.1% vs. 2.8%), and seizures (2.3% vs. 0.1%).[34]) The Patrick study has certain limitations.[35] Nevertheless, although the study's limitations prevent establishment of a direct relationship between opioid use and opioid-related NAS, the increases over time in both NAS and opioid use during pregnancy are clear. The Agency thus decided to raise the prominence of these warnings so that physicians and patients are better able to use the drugs safely — both for mothers, who may need opioid therapy during pregnancy, and for infants, who may need prompt recognition of and treatment for NOWS.

2. Other Statutory and Regulatory Requirements

The Petitions also assert that the NOWS-related labeling included in the SLC/PMR Letter – and, thus, presumably, the labeling that FDA approved on April 14, 2014 – is false and misleading, and is not based on "a fair evaluation of all material facts" (Citizen Petition at 3, 6-7; Petition for Stay at 2, 5-7).[36] For example, the Petitions allege that the labeling violates 21 CFR 201.56(a)(2) (requiring labeling to be "informative and accurate" and not false or misleading) and (a)(3) (stating that "labeling must be based whenever possible on data derived from human experience," and that "[n]o implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness") on the grounds that there "is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality" (Citizen Petition at 4). FDA disagrees with these assertions.

FDA has considered the new safety information discussed in the SLC/PMR Letter, other relevant publications, as well as the information supplied in the Petitions, and has concluded that the NOWS labeling approved on April 14, 2014 complies with applicable statutory and regulatory requirements. First, both the publications describing NOWS as "life-threatening"[37] and the Patrick study involve data derived from human experience. Second, the labeling language Petitioner contests ("[p]rolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome") is neither false nor misleading. In particular, the Agency has determined that NOWS can be life-threatening, and believes that the finalized labeling language is both informative, accurate, and not misleading — particularly when one reads all NOWS

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[34] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307 (18): 1934-30.

[35] Specifically, although the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes used in the analysis of maternal opiate exposures were specific to opioids, the ICD-9-CM code (779.5) used in the analysis of NAS was not specific to opioids. In addition, the data sources for NAS rate calculation and opioid use during pregnancy were unlinked. Petitioner also challenges the data from the Patrick study as, among other things, failing to distinguish between use of opioids as prescribed versus abuse or misuse and failing to reference the length of fetal opioid exposure. However, these concerns do not alter the Agency's continued reliance on the Patrick study in support of its NOWS labeling changes.

[36] The Petition contends that the NOWS-related labeling is not supported by "substantial evidence" as required by section 505(d)(5). However, substantial evidence is the standard for inclusion of information about effectiveness in the labeling. *See* FDCA 505(d)(5); 21 CFR 201.56(a)(3); Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

[37] *See, e.g.*, American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. Pediatrics 2012; 129:e540-e560; Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320-31.

sections of the new labeling, three of which state, "If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available."[38] This statement reflects FDA's recognition that ER/LA opioid analgesics may be necessary for some patients during pregnancy.[39] In addition, the ER/LA opioid analgesics' labeling as approved clarifies the risks NOWS presents, as it now includes the language: "[p]rolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which can be life-threatening **if not recognized and treated**" (emphasis added). This language emphasizes the importance of recognizing and treating NOWS as a part of neonatal care.

For the foregoing reasons, the language regarding NOWS in the labeling for ER/LA opioid analgesics complies with applicable statutory and regulatory requirements.[40]

C. Impact on Maternal and Fetal Health

Although the April 14, 2014 SLCs apply to ER/LA opioid analgesics, the Petitions' primary concern seems to be that the NOWS labeling may discourage opioid-addicted pregnant women from seeking or receiving addiction treatment, including OST. The Petitions also assert that the NOWS labeling "is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST" (Citizen Petition at 3, 11-15; Petition for Stay at 2, 11-15). The Citizen Petition thus requests several changes in the ER/LA opioid analgesics' labeling pertaining to both OST and NOWS.

FDA acknowledges the challenges faced by opioid-addicted pregnant women,[41] and agrees that OST can be an important component of their care. OST may also be important to fetal health, since abrupt opioid withdrawal during pregnancy can lead to fetal loss. FDA is not challenging the national and international guidelines[42] for care of opioid-addicted pregnant women, or the appropriate medical use of OST for these women during pregnancy. However, for the reasons discussed below, FDA declines to require the requested language as part of ER/LA opioid analgesics' labeling.

The Citizen Petition requests that FDA include the following language regarding OST in the ER/LA opioid analgesics' labeling (Petition at 2):

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[38] *See* the boxed warning in Highlights, the boxed warning, and section 5.3 of Warnings and Precautions.

[39] Notably, these drugs also are **not** contraindicated during pregnancy.

[40] *See* sections 505(d) and 505(o)(4) of the FD&C Act; 21 CFR 201.56, 57.

[41] Comments to the docket also have raised these concerns. *See, e.g.*, FDA-2013-P-1288-0005 (comment to the Citizen Petition docket).

[42] *See* American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012; Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. Treatment improvement protocol series 43. Substance Abuse and Mental Health Services Administration; 2005, revised 2012, available at: http://www.ncbi.nlm.nih.gov/books/NBK26113; World Health Organization, Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009). There are no national or international guidelines for opioid analgesia therapy during pregnancy, except for analgesia during labor. *See* American College of Obstetricians and Gynecologists Committee Opinion Obstetric analgesia and anesthesia. Number 36; July 2002.

- (1) Opioid dependence is a chronic, relapsing medical condition with high morbidity and significant risk of death. Opioid substitution treatment (OST) with methadone or buprenorphine is the best-proven way to reduce the harms of drug use for the individual and the community, including overdose, death and HIV infection. Persons found to be using [Tradename] without proper medical supervision or in a manner inconsistent with the prescribed dosage and/or duration should be encouraged to seek appropriate evaluation and treatment and offered assistance in doing so.

- (4) Opioid dependent pregnant women should be particularly encouraged to enter treatment since OST can lessen the risk of fetal demise and dramatically improve neonatal outcome. Physicians should be aware that infants born to mothers exposed to opioids during pregnancy for either medical or nonmedical purposes may be physically dependent on opioids and may develop an abstinence syndrome shortly after birth. Generally, this syndrome is readily recognized and treated, and is not associated with adverse long-term outcomes.

The suggested language in the first bullet (*i.e.*, suggested labeling paragraph (1)) above overstates the benefits of OST and fails to mention the risks of such treatment. Although FDA agrees that OST is an important method for managing opioid addiction, it is but one type of treatment. Nor is OST, in the absence of additional therapies, sufficient for all patients. Stating that "Opioid substitution treatment (OST) with methadone or buprenorphine is the best-proven way to reduce the harms of drug use..." would be an oversimplification of the management of opioid addiction.

In addition, FDA-approved labeling often alerts prescribers to risks associated with a drug without describing how to manage those risks. The labeling for ER/LA opioid analgesics, for example, informs prescribers about the risk of chronic pulmonary disease exacerbation, hypotension, raised intracranial pressure, worsened biliary tract disease, or aggravated seizures, but does not provide information about the treatment of these risks. FDA believes the approved labeling for the ER/LA opioid analgesics provides the essential scientific information that prescribers need in order to understand these risks, and the importance of identifying patients at risk and patients who begin to exhibit behaviors that may be associated with them.

The second suggested bullet (*i.e.*, suggested labeling paragraph (4)) above also overstates the benefits of OST, although for treatment of a labeled risk (addiction) in a specific population: pregnant women. Although FDA does not dispute the important role that OST may play in the care of opioid-addicted pregnant women, the Agency believes (as noted above) that the current labeling provides the essential scientific information for the safe use of these ER/LA opioid analgesics.

Suggested paragraph (4) also warns that babies born to opioid-dependent mothers may develop an abstinence syndrome – information that is already addressed in several places in the approved NOWS labeling – and a statement that NOWS is "readily recognized and treated, and is not associated with adverse long-term outcomes." However, based on a review of relevant published literature, FDA does not agree at this time that NOWS is not associated with long-term adverse consequences. Although available data regarding long-term risks of NOWS are limited, and more research should be done to evaluate the issue, there are suggestions in published literature that NOWS may be associated with substantive long-term effects on neurologic and cognitive

functioning.[43] Thus, at present, FDA is unable to conclude that NOWS "is not associated with adverse long-term outcomes."[44]

The Petition further requests that FDA replace section 5.3 of the Warnings and Precautions section of ER/LA opioid analgesic labeling with the following language:

- Infants born to mothers exposed to opioids during pregnancy, for medical or nonmedical purposes, may develop an abstinence syndrome shortly after birth. This syndrome, which can present as irritability, hyperactivity and abnormal sleep patterns, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight, generally is readily recognized and treated, and is not associated with adverse long-term outcomes.

- Opioid dependent pregnant women should be particularly encouraged to enter OST since this can lessen the risk of fetal demise and dramatically improve neonatal outcome.

(Petition at 2). Significantly, the NOWS labeling requested in the SLC/PMR Letter and approved on April 14, 2014 contains much of the language suggested in bullet 1, above. The exceptions are the statement that NOWS is "generally is readily recognized and treated, and is not associated with adverse long-term outcomes," and the language encouraging opioid-dependent pregnant women to use OST. This language is also suggested in the paragraph (4) labeling, FDA's response to which is discussed above.

For the foregoing reasons, FDA declines to require the requested language as part of ER/LA opioid analgesic labeling.

D. Request for Advisory Committee Review

Finally, the Citizen Petition requests that FDA present NOWS-specific literature reviews "justifying the labeling changes to an advisory committee so that the American public can be assured that any changes made to labeling will be evidence-based" (Citizen Petition at 3). FDA routinely assesses scientific literature and makes determinations regarding drug labeling, including pursuant to its SLC authority. Referring a matter to an advisory committee requires a substantial expenditure of resources and time, and the agency must prioritize these finite resources to the matters in which the agency would most benefit from the advice of outside

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[43] *See, e.g.*, Rosen TS and Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age *The Journal of Pediatrics* 1982; 101(2):192-196; Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders *Toxicology Letters* 2003; 140-141:171-181; Wahlsten VS and Sarman I. Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatrica* May 2013; 102(5):544-9.

[44] Again, the Agency notes that a risk does not need to have "long-term" consequences to be included in drug labeling.

experts.[45] FDA therefore declines to convene an advisory committee meeting regarding NOWS labeling at this time.

III. CONCLUSION

For the foregoing reasons, and as described above, the Petitions are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[45] *See* Draft Guidance for Industry: *Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings* at 4 (Aug. 2008). For example, FDA is likely to convene an advisory committee for a matter of "such significant public interest" or "so controversial" that advisory committee review is warranted, or if an advisory committee has a specialized expertise necessary for the agency's consideration.

Opioid abuse, dependence, and addiction in pregnancy. Committee Opinion No. 524. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:1070–6

http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Opioid-Abuse-Dependence-and-Addiction-in-Pregnancy

From the American Academy of Pediatrics: Clinical Report. Neonatal Drug Withdrawal.
Pediatrics Vol. 129 No. 2 February 1, 2012
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http://pediatrics.aappublications.org/content/129/2/e540

Guidance
Drug Safety Information – FDA's Communication to the Public

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Edward Staffa 301-796-5301, or (CBER) Office of Communication, Outreach and Development at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2012
Drug Safety

Revision 1

Guidance

Drug Safety Information – FDA's Communication to the Public

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Drug Safety

Revision 1

TABLE OF CONTENTS

Guidance[1]
Drug Safety Information – FDA's Communication to the Public

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

INTRODUCTION

This guidance explains how FDA develops and disseminates information to the public about important drug safety issues, including emerging drug safety information.[2] Timely communication of important drug safety information provides health care professionals, patients, consumers, and other interested persons with access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed treatment choices.

This guidance revises the March 2007 guidance, *Drug Safety Information – FDA's Communication to the Public*[3] by providing updated information about FDA's approach to communicating important drug safety information. The revised guidance describes the Center for Drug Evaluation and Research's (CDER's) single, standardized format for electronic drug safety communications about marketed drugs and provides information about the Center for Biologics Evaluation and Research's (CBER's) safety communication activities. In addition, the revised guidance describes FDA's posting of other safety assessments on its Web site in accordance with the requirements of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and to further our transparency objectives. When finalized, this guidance will replace the 2007 guidance.

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[1] This guidance has been prepared by the Office of Communications in the Center for Drug Evaluation and Research (CDER) in consultation with CDER's Safety First Steering Committee at the Food and Drug Administration and in cooperation with the Center for Biologics Evaluation and Research (CBER).

[2] For purposes of this guidance, all references to *drugs* include both human drugs and biological drug products. This guidance does not apply to human cells, tissues, and cellular and tissue-based products regulated solely under section 361 of the Public Health Service Act.

[3] We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidances (Drugs) page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm. Although this guidance addresses drug safety communications in general, it is not meant to be a comprehensive description of our communications for the wide range of products regulated by FDA (e.g., vaccines). FDA's Web site contains more specific information for certain classes of products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

BACKGROUND

All drugs have risks, and health care professionals and patients must balance the risks and benefits of a drug therapy when making decisions about whether to use the drug. The general risks and benefits of a drug therapy are described in the product's prescribing information. In addition, however, FDA provides information on drug risks and benefits to health care professionals and patients when that information has generated a specific concern, usually waiting until that information has been fully evaluated and has prompted a regulatory action, such as a revision to the drug's prescribing information. In recent years, FDA has begun making information on potential drug risks available to the public earlier — often while the Agency is still evaluating the data and determining whether any regulatory action is warranted. FDA believes that timely communication of important drug safety information will give health care professionals, patients, consumers, and other interested persons access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed individual treatment choices.

The following questions and answers provide general guidance on how FDA communicates important safety information to the public.

QUESTIONS AND ANSWERS

1. What Is This Guidance About?

This guidance describes how FDA develops and disseminates information to the public about important drug safety issues, including emerging drug safety information. As discussed in more detail below, an *important drug safety issue* is one that has the potential to alter the benefit–risk analysis for a drug in such a way as to affect decisions about prescribing or taking the drug. Examples of important drug safety issues include, but are not limited to:

- Serious adverse drug reactions identified after drug approval

- Medication errors, which include, but are not limited to, confusion between drug names and confusion regarding drug labeling. These may lead to improper use of the drug, to prescribing or administering an improper dose, or to a patient's taking another medication with which the drug interacts.

We use the term *emerging drug safety information* to describe information FDA is monitoring or analyzing that may have the potential to alter the benefit–risk analysis for a drug in a way that would affect decisions about prescribing or taking the drug, but that has not yet been fully analyzed or confirmed. Such information may relate to new risks or new information about known risks.

FDA may disseminate important drug safety information by other methods and at other times than those described in this guidance. For example, FDA may decide to issue a Public Health Alert or a press release about a medical product or hold a media briefing to communicate important risk information.

2. How Does FDA Evaluate Drug Safety Information?

FDA monitors and reviews safety information about a drug throughout the product's lifecycle, interacting with sponsors during product development and clinical investigation of the drug, closely reviewing safety issues during consideration of a marketing application, and, if the drug is approved, monitoring safety reports after the drug is marketed. Every approved drug has labeling (e.g., prescribing information) that contains, among other things, information about the benefits and risks of using the drug.

After drug approval, FDA may learn of new, or more serious or more frequent, adverse drug reactions from, for example, postapproval voluntary or mandatory reporting of adverse drug reactions during use of the drug, postapproval clinical trials exploring new uses of the drug, other postapproval studies including epidemiologic studies or active surveillance evaluations. For example, additional adverse drug reactions, some of them serious, may be identified once a drug is used more widely and under more diverse conditions (e.g., concurrent use with other drugs), or when the drug is prescribed for off-label uses. In some cases, medication errors can occur because of name confusion or other factors that influence safe use of the medication.

As new information related to a drug becomes available, the Agency reviews the data and evaluates whether there is an emerging drug safety concern. When such a concern arises, relevant medical and scientific experts within FDA engage in a prompt review and analysis of available data. Often, however, there is a period of uncertainty while FDA evaluates the emerging safety information to determine whether there is an important drug safety issue related to a specific drug or drug class and whether regulatory action is appropriate and, if so, what type of action is necessary.[4]

[4] FDA recently issued a draft guidance to FDA staff for comment on *Classifying Significant Postmarket Drug Safety Issues.* This guidance describes the methodological framework by which FDA will classify significant postmarket drug safety issues as *priority*, *standard*, or *emergency*. This guidance is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The draft, when finalized, will reflect the Agency's current thinking on this issue.

During this period, FDA also is actively engaged in scientific efforts to gather additional safety information. Drug sponsors[5] also gather and evaluate emerging safety information and provide the results of their analyses to FDA. As additional data relevant to an emerging drug safety issue become available (e.g., data from an ongoing study or trial, data from surveillance evaluations, or data from available clinical databases), these data are considered in the analysis and decision-making process. FDA may decide that, based on evaluation of additional data related to the drug, further regulatory action, such as requiring a revision to prescribing information or a Risk Evaluation and Mitigation Strategy (REMS), may be appropriate.

Interpreting postmarket safety data is complex, involving analysis of clinical data and detailed review of a wide range of potentially relevant information, including adverse drug experience spontaneous reports, pertinent controlled clinical trials and epidemiologic studies, active surveillance efforts, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information. Decisions about how to address a safety concern often are a matter of judgment about which reasonable and adequately informed persons with relevant expertise may disagree. We engage in robust and comprehensive discussions within the Agency regarding potential drug safety issues to ensure that all points of view are considered before making a decision on how to proceed.[6] We may consult the Drug Safety Oversight Board, established by FDA in February 2005, asking it to provide recommendations to the center director regarding the management and communication of an emerging drug safety issue.[7] We also may engage in external discussions by convening an Advisory Committee, or coordinating with other public health agencies, such as the Centers for Disease Control and Prevention, or the National Vaccine Program Office, regarding an emerging drug safety issue.

As the Agency evaluates a drug safety issue to determine whether regulatory action is warranted, we may decide to communicate further information to the public at appropriate points during the decision-making process. Consistent with our public health mandate, we may advise the public of an emerging drug safety concern as well as the next steps the Agency may take regarding an important drug safety issue, and there may be updates to this information.

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[5] The term *sponsor* is used broadly in this guidance to refer to the individual or entity that markets a drug or that takes responsibility for and initiates a clinical investigation of a drug. Usually, the sponsor is the owner of the application (*application holder*) for the drug. The *sponsor* also might be the manufacturer of the drug.

[6] See the Manual of Policies and Procedures (MAPP) 4151.1, *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*, Revision 1, effective September 16, 2010; MAPP 4151.2, *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director*, Revision 1, effective September 16, 2010; and MAPP 4151.8, *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*, effective September 16, 2010. These MAPPs can be accessed at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm. See also the CBER Standard Operating Procedure and Policy (SOPP) 8006: Resolution of Differences in Scientific Judgment in the Review Process, Version #2, effective January 15, 2009, available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109584.htm.

[7] The DSB was subsequently established by statute as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA), creating section 505-1(j) of the Federal Food, Drug, and Cosmetic Act.

3. When Does FDA Communicate Emerging Drug Safety Information to the Public?

FDA currently disseminates emerging drug safety information after having completed an analysis of available data and, in some cases, before having reached a decision about whether regulatory action is warranted. FDA communications about emerging drug safety information can help achieve certain long-standing public health goals, including enhanced vigilance on the part of health care professionals who also may be prompted to increase their reporting of safety observations to FDA.

FDA recognizes the potential public health implications of providing emerging drug safety information, and we are particularly concerned about possible unintended consequences, such as inappropriate modification or discontinuation of useful treatment. We attempt to anticipate and address these possible consequences through our risk communications by (1) describing the nature of a safety concern and what is known about its relationship to a particular drug and (2) making recommendations for health care professionals and patients about how to monitor for and manage the concern.

With respect to potentially important information, the dual goals of having people informed as early as possible and having that information thoroughly substantiated inevitably creates tension. Despite this tension, we lean toward early communication of emerging drug safety information unless, in our judgment, the information available is not reliable enough to be useful and could mislead the public. We recognize this means that, in some cases, we will have to say that a safety concern "has not yet been substantiated." Our goal is to make emerging drug safety information available to the public in a balanced, impartial manner so that health care professionals and patients can consider the information when making decisions about medical treatment, despite uncertainties in the data. FDA is committed to providing accurate, clear, reliable, and useful drug safety information.

FDA considers many factors in the course of evaluating an emerging drug safety issue and deciding whether emerging drug safety information should be made available to the public. These factors may include, but are not limited to, the following:

- Seriousness of the event (e.g., severity and reversibility) relative to the benefits of treatment
- Magnitude of the risk (e.g., likelihood of occurrence)
- Strength of the evidence of a causal relationship between the use of a drug and the adverse event[8]
- Extent of patient exposure (e.g., how broadly the drug is used)
- Disproportionate impact on particular populations (e.g., children or the elderly)

[8] See, for example, guidance for industry on *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* at pages 6 to 7 and 17 to 18, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- Potential for preventing or mitigating the risk in the patient population (e.g., by monitoring patient selection or avoiding a concomitant treatment)
- Availability of alternative therapies

The decision to provide information about an emerging drug safety issue does not necessarily mean that FDA has concluded there is a causal relationship between the drug and the adverse event described. Nor does communicating emerging drug safety information necessarily mean that FDA is advising health care professionals to limit their prescribing of the drug at issue. Rather, the communications are intended to further inform prescribing and assist health care professionals in making individualized treatment decisions with their patients, based on the balance of potential benefits and risks of the drug for that patient.

At times, decisions to communicate about important drug safety issues are affected by information the public has received from sources other than FDA, such as the mainstream media. In these cases, the safety of a particular drug or drug class may be publicly questioned based on information provided by these other sources that may be incorrect, incomplete, or misleading. In such cases, FDA may issue a statement or engage in other methods of communication to clarify or correct information and respond to public interest.

FDA strives to keep all communications clear and understandable. We also consider elements of human behavior in our communications. We realize, for instance, that risk information provided without context may alarm patients, causing them to discontinue needed medication. With all drug safety communications, FDA now makes a concerted effort to communicate the benefits of a drug along with its risk. Whenever possible and appropriate, when we communicate drug safety information, we include specific advice to patients who use the drug on its safe and effective use to facilitate discussions with their health care practitioners.

4. How Does FDA Communicate Important Drug Safety Information to the Public?

FDA has created effective and ongoing relationships with a wide array of trade and professional associations, patient advocacy and consumer groups, safety organizations, media, and other entities. When drug safety issues arise, we reach out to these groups and work with them to communicate the safety issue to their constituencies.

FDA uses various tools and methods to communicate drug safety information to the public. Important tools used in this effort include, but are not limited to, FDA-approved prescribing information (i.e., drug labeling) and a postmarket communication tool called a *Drug Safety Communication* (DSC), both discussed in the following questions, along with other important tools and methods we use to communicate drug safety information to the public.

5. What is FDA-Approved Labeling?

FDA-approved prescribing information for health care professionals — and patient package inserts and Medication Guides for patients — is the primary source of established information about a drug's safety and efficacy; it summarizes the essential scientific information needed for

the safe and effective use of the drug. The prescribing information for prescription drugs contains sections directed to health care professionals, and may also include sections that are intended for patients.[9]

For some prescription drugs, such as oral contraceptives and estrogens, FDA long ago determined that the safe and effective use of the drug required additional information in nontechnical language to be distributed directly to patients by their health care practitioner or pharmacist (21 CFR 310.501 and 310.515). These *patient package inserts* also may be provided voluntarily by manufacturers for other drugs and are regulated by FDA as labeling.

When patient-directed information is considered necessary for proper use of a drug, FDA requires patient-oriented information in nontechnical language in the form of *Medication Guides* (MedGuides). These have been required for certain prescription drugs that pose a serious and significant public health concern and for which FDA-approved patient information is necessary for safe and effective use of the drug. MedGuides are required if FDA determines that one or more of the following circumstances exist:

- Patient-focused information (*patient labeling*) could help prevent serious adverse effects.
- A drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect a patient's decision to use, or to continue to use, the product.
- A drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.[10]

In addition, over-the-counter (OTC) drugs bear a *Drug Facts* label that conveys information in a clear, standardized format to enable consumer self-selection of an appropriate drug and enhance the safe and effective use of the drug by consumers.[11]

FDA-approved prescribing information for CDER-regulated drug products is available on the FDA Web site at *Drugs@FDA*. FDA-approved prescribing information for CBER-regulated products is available on the FDA Web site.[12] In addition, FDA facilitates the availability of up-to-date drug prescribing information in an easily accessible electronic format on the National Library of Medicine Web site at *DailyMed*.[13] See also question 10.

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[9] In the *Federal Register* of January 24, 2006 (71 FR 3922), FDA published a final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," designed to improve the usefulness of prescribing information for prescription drugs approved after June 30, 2001 (for further information, see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm). Labeling for these drugs is currently being converted to the new content and format according to a schedule determined at the time of publication of the final rule, and is expected to facilitate the safe and optimal use of prescription drugs.

[10] See 21 CFR 208.1.

[11] See 21 CFR 201.66 (format and content requirements for over-the-counter (OTC) drug product labeling).

[12] See http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm.

[13] See http://dailymed.nlm.nih.gov/dailymed/about.cfm.

6. What is a CDER Drug Safety Communications (DSC)?

A *Drug Safety Communication* (DSC) is a specific tool used by FDA to communicate to the public important information about safety issues, including emerging safety information, about marketed drugs. DSCs are standardized electronic communications posted on the FDA Web site.[14] Written as clearly as possible, DSCs are targeted to both health care professionals and patients. DSCs generally communicate the following information:

- A summary of the safety issue and the nature of the risk being communicated
- The established benefit or benefits of the drug being discussed
- Recommended actions for health care professionals and patients, when appropriate
- A summary of the data reviewed or being reviewed by FDA

The DSC is FDA's primary safety communication tool for important postmarket drug safety issues. In the past, and at the time our March 2007 guidance was released on this topic, safety communications were issued by FDA in a variety of formats. They were issued under different titles and targeted to different audiences. For instance, in August 2007, FDA began issuing *Early Communications about Ongoing Safety Reviews* (ECs) to keep health care professionals and the general public informed of postmarket safety issues under evaluation by FDA. Safety communications have also been issued under the titles *Public Health Advisory*, *Patient Information Sheet*, *Healthcare Professional Sheet*, and *Alerts on Patient Information and Healthcare Professional Sheets*, and, as these titles suggest, have targeted different audiences. To improve the clarity of our communications, FDA began using a single communication vehicle — the *Drug Safety Communication* — in early 2010.

Some DSCs are related to drug safety issues that continue to develop as more information is obtained. FDA disseminates follow-up DSCs to keep the public informed of new information pertaining to a previously communicated DSC. In addition, some emerging safety information may take a long time to evaluate (if, for example, there is a need for additional clinical trial or epidemiological data to further assess the risk). During the evaluation period, FDA may issue a follow-up DSC as a public reminder, even if no additional information is available since the original DSC was issued.

Note: Although a DSC communicates important safety issues about marketed drugs, it is ***not*** a crisis communication document. If a drug product is defective or tainted, or poses some other form of immediate danger, FDA uses other communication tools, such as *Public Health Alerts*, press releases, stakeholder calls, and media briefings, to inform the public rapidly and protect public health.

7. How Does CBER Communicate Safety Information?

FDA's Center for Biologics Evaluation and Research (CBER) communicates important postmarket safety information regarding biological products to the public using the most

[14] See at http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm.

appropriately targeted communication, taking into consideration the type of product (e.g., vaccine, blood product, or cell therapy), safety issue, and audience. Examples of communication tools include Public Health Notifications, press releases, and safety information updates. These safety communications, like DSCs noted above, include the following important information: (1) a summary of the safety issue and FDA's current understanding of the risk; (2) a summary of information, including the source of the information, reviewed by FDA; (3) information on the benefits and risks of the product involved; and (4) when available and appropriate, recommendations for health care professionals and/or patients and caregivers. Follow-up information is disseminated to keep the public informed of new information pertaining to a previously communicated safety issue. CBER may issue a follow-up as a public reminder, even if no additional information is available since the original communication was issued.

As with CDER-regulated products, if a CBER-regulated biological product is defective or tainted, or poses some other form of immediate danger, FDA may choose from a variety of other communication tools and channels to rapidly inform the public and protect public health.

8. What Other Safety Information Does FDA Post on Its Web Site?

In accordance with requirements of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and to further our transparency objectives, FDA posts various other types of drug safety information, in addition to DSCs, on its Web site, including the following:[15]

- Since 2008, as required by section 921 of FDAAA, FDA has posted on its Web site reports of potential safety issues with drugs[16] identified as a result of our reviews of reports to FDA's Adverse Event Reporting System (AERS). The appearance of a drug on this list, which is updated quarterly, means that FDA has identified a potential safety issue (i.e., new safety information or a potential signal of a serious risk), but it does not mean that FDA has concluded there is a causal relationship between the drug and the risk described.[17]

- Since June 16, 2010, FDA has been posting the results of evaluations performed in accordance with section 915 of FDAAA. Section 915 requires FDA to evaluate marketed drugs 18 months after approval or after 10,000 individuals have used the drug, whichever is later. These evaluations are conducted using various sources of available safety information about marketed drugs to determine whether there are any new serious adverse events not previously identified during development, known side effects reported

[15] This is not an all inclusive list but highlights some new categories of drug safety information we have begun to post as required by FDAAA.

[16] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM082196.

[17] FDA has used the term *safety signal* to refer to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. See FDA guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

in an unusual number of patients, or potential new safety concerns now that the drugs are being used in the general population.[18]

- In accordance with section 915 of FDAAA, FDA maintains a list of drugs that have been approved with Risk Evaluation and Mitigation Strategies (REMS) and copies of those REMS on its Web site.[19]

9. What Other Methods Are Used to Communicate Drug Safety Information?

In addition to written communications, FDA uses other communication tools, including webinars, broadcasts, and conference calls, to disseminate drug safety information. FDA uses various forms of electronic social media to communicate some safety issues and is continuing to assess additional ways to communicate effectively with the public using these vehicles.

Consistent with FDA's commitment to the expansion of existing communication channels to provide targeted drug safety information to the public, FDA is exploring additional methods of communication, including concise advisories and other Internet postings; more detailed short articles; articles in trade and professional journals; a standardized, one-document solution for patient medication information (PMI); and background papers. If new communication tools are adopted, we intend to update this guidance.

Drug sponsors also use various methods to communicate drug safety information. For example, a sponsor might distribute a Dear Health Care Provider Letter (sometimes referred to as a *Dear Doctor* letter) to convey important information about a marketed drug. A sponsor can issue a Dear Health Care Provider Letter on its own initiative or following a request or requirement by FDA. A sponsor can be required to issue a Dear Health Care Provider Letter or other communication that is approved as part of a communication plan of a REMS. Dear Health Care Provider letters can be used to disseminate information regarding a significant hazard to health, to announce important changes in prescribing information, or to emphasize corrections to prescription drug advertising or prescribing information. Depending on the issue and whether the communication is tied to a regulatory action, FDA may notify the public when sponsors issue a Dear Health Care Provider Letter.

10. Where Is FDA's Drug Safety Information Located?

All of the drug safety information FDA communicates is available via links found on FDA's Web site (e.g., links to the Index to Drug-Specific Information Web page, Drugs@FDA, Safety and Availability [Biologics] and MedWatch Web pages), as described below.

FDA's Web site provides an easily accessible link to the Index to Drug-Specific Information Web page (http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm) from which the public can access information about drugs that are the subject of a DSC regarding an important, and often

[18] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm.

[19] See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

emerging, drug safety issue, as well as established drug safety information. This Index contains links to available Drug Information Pages for specific drugs (identified by both trade name and nonproprietary name) that contain approved drug prescribing information, consumer-friendly information sheets, when available, and other drug information. Drug Information Pages generally are available for drugs that are new molecular entities, or that have been the subject of recent safety communications.

For drugs without a Drug Information Page, the Web page links consumers to Drugs@FDA, which contains drug prescribing information and other regulatory information related to approved drugs (see http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

FDA's Web site contains the Safety & Availability [Biologics] page from which the public can access information about CBER-regulated drugs that are the subject of an important safety communication. (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/default.htm). In addition, product information pages for licensed biological products include links to related safety information.

The MedWatch program augments FDA and manufacturer communication of drug safety information by distributing MedWatch Safety Alerts to individual subscribers and through its MedWatch Partners Program. Safety information about medical products (including drugs, biologics, devices, and dietary supplements), such as selected information that is the subject of Drug Safety Communications, Dear Health Care Provider Letters, press releases, and market withdrawals, also is available through MedWatch Safety Alerts. This information is available to the general public on the MedWatch Web site (http://www.fda.gov/medwatch/safety), which contains archived information dating back to 1996.

MedWatch, in addition to sending out individual medical product alerts, posts Monthly Safety Labeling Changes on the Web and also distributes them via an alert.[20] This posting includes clinically important prescribing information updates to the following sections of the prescribing information:

- Boxed Warnings
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Patient Package Insert & Medication Guide

11. How Is Drug Safety Information Updated?

The public can access the most current safety information about a drug through the Index to Drug-Specific Information and Safety & Availability [Biologics] Web pages. FDA intends to update the information available on these Web pages on a periodic basis to reflect new information that becomes available.

[20] See http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm.

Emerging drug safety information presented as a DSC is identified by the month and year in which the information is posted on the Index to Drug-Specific Information Web page. We intend to update DSCs to describe important new information relevant to the emerging drug safety issue after the emerging drug safety issue is addressed through revision of prescribing information, approval of a REMS, request for voluntary withdrawal from the market, or other regulatory action. We plan to identify updated information with the month and year in which it was added to the Web site or communicated by other methods. After an emerging safety issue has been addressed through regulatory action, it is permanently archived (as are all DSCs) on the FDA Web site.

If data become available that provide sufficient evidence that a drug is not associated with the safety concern previously described by FDA as an emerging drug safety issue, FDA intends to update the information accordingly. In these instances, we plan to issue a new update of comparable prominence to the DSC to reflect this new information. Updated DSCs, like all DSCs, are permanently archived on the Web site.

Some important drug safety information may have utility independent of any regulatory action. For example, sometimes a sponsor may be required to conduct a long-term study or clinical trial related to an emerging drug safety issue.[21] This is one reason why DSCs remain permanently archived.

FDA recognizes that evaluation of some emerging drug safety issues may not be accomplished quickly. This may be because of the complexity of an issue or the need for studies or clinical trials of adequate duration to evaluate a potential risk with a long latency period.[22] In these cases, archived DSCs create a permanent record of the continued evaluation of the issue. This will help ensure that important information about ongoing safety issues that may affect a health care professional's decision to prescribe, or a patient's or consumer's decision to use, a medication will continue to be communicated.

For CBER-regulated products, emerging drug safety information is presented on FDA's Web page Safety & Availability [Biologics] by the year in which the information is posted. Updates are provided as new information becomes available.

12. How Does FDA Handle Confidential Information About a Drug Safety Issue?

Most of the information currently posted on the Index to Drug-Specific Information Web page is information that is prepared for public disclosure and contains no confidential information. FDA may publish related information on the Web page that was not specifically prepared for public disclosure, such as FDA scientific reviews. This information is reviewed before publication to ensure that disclosure of this information is in accordance with applicable disclosure laws and FDA regulations.

[21] See 21 U.S.C. 355(o)(3).

[22] See draft guidance, *Classifying Significant Postmarket Drug Safety Issues*.

13. Does FDA Involve Sponsors Before Making Emerging Drug Safety Information Public?

Our communication of emerging drug safety information is intended to represent FDA's independent analysis of emerging information and FDA's scientific judgment as to the appropriate communication of this emerging drug safety information to the public. FDA may solicit sponsor input when appropriate, for example, to confirm the accuracy of factual information. FDA strives to notify the relevant sponsor at least 24 hours before the first public communication that emerging safety information about its drug will be posted on the FDA Web site.

For purposes of this guidance, the relevant sponsor generally is the new drug application (NDA), biologics license application (BLA), or abbreviated new drug application (ANDA) holder(s) for the drug or drug class that is the subject of a DSC containing an important drug safety issue. We recognize that over-the-counter (OTC) drugs subject to one or more final OTC monographs, rather than approved under an NDA or ANDA, may be manufactured by multiple entities and thus have multiple relevant sponsors. FDA continues to consider appropriate mechanisms to facilitate timely notification of affected entities marketing OTC drugs and welcomes comment on this issue.

Note: Sponsors are required to report certain adverse drug experience information to FDA in accordance with the U.S. Food, Drug, and Cosmetic Act (FDCA) and our regulations[23] and may provide FDA with additional information relevant to a drug safety issue at any time. A sponsor also may request that the Agency update its communication of emerging drug safety information if the sponsor provides additional information supporting the request.[24]

14. Can FDA Risk Communication Be Used in Prescription Drug Promotion?

FDA recognizes that some sponsors may consider making promotional comparisons between their drugs and drugs for which emerging drug safety information has been provided by FDA. We remind sponsors that all safety and effectiveness claims made in prescription drug promotion,[25] including claims based on Government materials available from the Index to Drug-Specific Information, must be supported by substantial evidence or substantial clinical experience and must not be otherwise false or misleading (21 U.S.C. 355 and 352; 21 CFR 202.1(e)).

[23] Sponsors of approved NDAs or ANDAs, manufacturers of marketed prescription drugs for human use without approved NDAs or ANDAs, and licensed manufacturers of approved BLAs are required to report adverse experiences to the FDA under 21 CFR 310.305, 314.80, 314.98, and 600.80. Manufacturers of OTC products subject to monographs are required to report serious adverse experiences to the FDA under FDCA section 760.

[24] Any such request should be made in accordance with standard procedures for submitting information concerning a particular drug to FDA (e.g., directed to the appropriate division within the Office of New Drugs, the Office Generic Drugs, or the Office of Nonprescription Products, as appropriate).

[25] The Federal Trade Commission (FTC) has primary responsibility for regulating the advertising of nonprescription drug products.

Neither the fact that FDA has communicated emerging drug safety information for a drug nor the specific information posted about that drug will generally constitute (either separately or collectively) substantial evidence or substantial clinical experience that would support a comparative safety or effectiveness claim. Therefore, comparative claims made in prescription drug promotion based on an FDA communication of emerging drug safety information (e.g., "Our drug is safer because of the emerging drug safety information posted by the FDA about a competitor's drug") may be considered false or misleading.

Representations that minimize the implications of emerging drug safety information communicated by FDA also may be considered false or misleading. For those seeking to explain to health care professionals what emerging drug safety information means, we refer to the sections of this guidance that discuss the purpose of disseminating emerging drug safety information and the nature of the information to be posted on the Index to Drug-Specific Information Web page.

SUMMARY

FDA plays a critical role in detecting and managing safety issues that are identified after a drug is approved for marketing, including a critical role in communicating information to the public. The actions we take depend on many factors, including the characteristics of the adverse events, the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a benefit, the availability of alternative therapies, and the consequences of not treating the disease. Despite working toward systematic methods of identifying and disseminating information about drug safety issues, communicating about drug safety issues will always require a significant amount of judgment about whether to communicate in a given case and, if so, what to communicate.

It is our goal is to make the most up-to-date drug safety information available to the public in a timely manner so that health care professionals and patients can consider the information when making decisions about medical treatment, yet be aware of uncertainties in the data. FDA is committed to providing accurate, clear, reliable, and useful drug safety information.

Methadose™ Oral Concentrate
(methadone hydrochloride oral concentrate USP)
and
Methadose™ Sugar-Free Oral Concentrate
(methadone hydrochloride oral concentrate USP)
dye-free, sugar-free, unflavored

CII

Rx only

FOR ORAL USE ONLY

Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration (see DOSAGE AND ADMINISTRATION). Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone,

although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8

METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY. CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

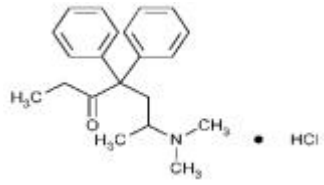
1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.

2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

DESCRIPTION

Methadose™ Oral Concentrate (methadone hydrochloride USP) is supplied as a cherry flavored liquid concentrate. Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride USP) is a dye-free, sugar-free, unflavored liquid concentrate of methadone hydrochloride. Each liquid concentrate contains 10 mg of methadone hydrochloride per mL.

Methadone hydrochloride is chemically described as 3-heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride. Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in Methadose as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 part per 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO \cdot HCl$ and its structural formula is:



Other ingredients of Methadose Oral Concentrate: Artificial cherry flavor, citric acid anhydrous USP, FD&C Red No 40, D&C Red No 33, methylparaben NF, polaxamer 407 NF, propylene glycol USP, propylparaben NF, purified water USP, sodium citrate dihydrate USP, sucrose NF.

Other ingredients of Methadose Sugar-Free Oral Concentrate: Citric acid anhydrous USP, purified water USP, sodium benzoate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a mu agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are analgesia and detoxification or maintenance treatment in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to a_1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life ($T_{1/2}$) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy

The disposition of oral methadone has been studied in approximately 30 pregnant patients in the second and third trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is

decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone. (See PRECAUTIONS: Pregnancy, Labor and Delivery, and DOSAGE AND ADMINISTRATION.)

Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the elimination of methadone or its metabolites.

Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race

The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric

The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric

The pharmacokinetics of methadone have not been evaluated in the pediatric population.

Drug Interactions

(see PRECAUTIONS: Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

INDICATIONS AND USAGE

1. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).

2. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Methadose is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadose.

Methadose is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

Methadose and Methadose Sugar-Free are for oral administration only. The preparation must not be injected. Methadose and Methadose Sugar-Free, if

dispensed, should be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Respiratory Depression

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and central nervous system (CNS) depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Methadone should be used at the lowest effective dose and only under careful medical supervision.

Cardiac Conduction Effects

This information is intended to alert the prescriber to comprehensively evaluate the risks and benefits of methadone treatment. The intent is not to deter the appropriate use of methadone in patients with a history of cardiac disease.

Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT

interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities and drugs which might act as inhibitors of methadone metabolism.

The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone

should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

When treating patients with methadone, an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to be at risk, careful monitoring of cardiovascular status, including evaluation of QT prolongation and dysrhythmias should be performed.

Incomplete Cross-tolerance between Methadone and other Opioids

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other mu-opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Misuse, Abuse, and Diversion of Opioids

Methadone is a mu-agonist opioid with an abuse liability similar to that of morphine and other opioid agonists and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when dispensing Methadose in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion. Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS).

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (e.g., severe volume depletion).

PRECAUTIONS

Methadose should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive.

Drug Interactions

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, and lopinavir+ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists

As with other mu-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-retroviral Agents

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine – Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine – Experimental evidence demonstrated that methadone increased the AUC of zidovudine which could result in toxic effects.

Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin – In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin – In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal

symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine

Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin), should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole – Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 4 days) increased the Cmax and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). The Cmax and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity, including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others

Monoamine Oxidase (MAO) Inhibitors – Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine – Plasma levels of desipramine have increased with concurrent methadone administration.

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing Methadose concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety – Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients will react to life

problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain – Patients in methadone maintenance treatment for opioid dependence who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Physical Dependence

Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence is expected during opioid agonist therapy of opioid addiction.

If a physically dependent patient abruptly discontinues use of methadone, or the dose of methadone does not adequately "cover" the patient, an opioid abstinence or withdrawal syndrome may develop and is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms may also develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see PRECAUTIONS: Pregnancy, Labor and Delivery).

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: For Medically Supervised Withdrawal After a Period of Maintenance Treatment).

Special-Risk Patients – Methadone should be given with caution, and the initial dose reduced, in certain patients such as the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression requires added vigilance.

Information for Patients

- Patients should be cautioned that Methadose, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients who are ambulatory should be cautioned that Methadose, like other opioids, may produce orthostatic hypotension.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking Methadose.
- Patients initiating treatment with Methadose should be reassured that the dose of methadone will “hold” for longer periods of time as treatment progresses.

- Patients should be instructed to keep Methadose in a secure place out of the reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death.
- Patients should be advised not to change the dose of Methadose without consulting their physician.
- Women of childbearing potential who become or are planning to become pregnant should be advised to consult their physicians regarding the effects of Methadose use during pregnancy.
- If a physically dependent patient abruptly discontinues use of Methadose, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the methadone dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Patients seeking to discontinue treatment with Methadose for opioid dependence should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.
- Patients should be advised that Methadose is a potential drug of abuse. They should protect it from theft, and it should never be taken by anyone other than the individual for whom it was prescribed.
- Breastfeeding:

    1. Methadone use is usually compatible with breastfeeding. Pregnant mothers using methadone should be counseled about the benefits and risks of breastfeeding while using methadone. Counseling should include the following information:

- The baby receives a small amount of methadone through breastmilk.
- The baby may experience methadone withdrawal if breastfeeding is discontinued suddenly. Patients discontinuing breastfeeding should develop a plan to wean with the baby's healthcare team.
- Use of other substances of abuse during breastfeeding will expose the baby to additional risks. Patients who use other substances of abuse should not breastfeed.

2. When starting methadone for the first time or increasing the dose, breastfeeding patients should watch their babies closely for changes in behavior or breathing patterns.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis – The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m^2). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the

assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis – There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the in vivo mouse dominant lethal assay and the in vivo mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naive female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

Pregnancy

Teratogenic Effects – *Pregnancy Category C.* There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised,

therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as “limited to fair”). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the second trimester or premature delivery in the third trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately twice a human daily oral dose of 120 mg/day on a mg/m2 basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m2 basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m2 basis) administered during Days 6 to 15 and 6 to 18, respectively.

Nonteratogenetic Effects – Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rats that were treated with methadone prior to mating. In these studies, the female rats were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Furthermore, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of “paternal” methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology in Pregnancy – Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with Methadose. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Nursing Mothers

Methadone is secreted into human milk. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone.

Caution should be exercised when methadone is administered to a nursing woman. There have been rare cases of sedation and respiratory depression in infants exposed to methadone through breast milk.

Mothers using methadone should receive specific information about how to identify respiratory depression and sedation in their babies. They should know when to contact their healthcare provider or seek immediate medical care. A healthcare provider should weigh the benefits of breastfeeding against the risks of infant exposure to methadone and possible exposure to other medicines.

Women being treated with methadone for any indication who are already breastfeeding should be counseled to wean breastfeeding gradually in order to prevent the development of withdrawal symptoms in the infant.

Methadone Maintenance Treatment for Opioid Dependence during Breastfeeding

Women on methadone maintenance therapy, who express a desire to breastfeed, should be informed of the risks and benefits of breastfeeding during pregnancy and immediately postpartum. The patient should clearly understand that, while breastfeeding, she should not use illicit substances or any other drug not prescribed by her healthcare provider. She should understand the reasons why use of additional drugs can increase risk to her breastfeeding infant beyond any risk from methadone.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and caregivers should be instructed to keep Methadose in a secure place out of the reach of children and to discard unused

methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects.

They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following: (listed alphabetically under each subsection)

Body as a Whole – asthenia (weakness), edema, headache

Cardiovascular (also see **WARNINGS: Cardiac Conduction Effects**) – arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

Nervous – agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures

Respiratory – pulmonary edema, respiratory depression (see WARNINGS: Respiratory Depression)

Skin and Appendages – pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses – hallucinations, visual disturbances

Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy

Maintenance on a Stabilized Dose – During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Methadose contains methadone, a potent Schedule II opioid agonist. Schedule II opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. **Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.**

Abuse of Methadose poses a risk of overdose and death. This risk is increased with concurrent abuse of Methadose with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Since Methadose may be diverted for non-medical use, careful record keeping of ordering and dispensing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Methadose, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (and agencies, practitioners or institutions by formal agreement with the program sponsor).

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (See PRECAUTIONS; Pregnancy, Labor and Delivery).

OVERDOSAGE

Signs and Symptoms

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.**

While methadone's duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). **Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects.** Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

Detoxification and Maintenance Treatment of Opiate Dependence

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Induction/Initial Dosing

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will “hold” for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

For Short-term Detoxification

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 to 3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but

the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed.

For Maintenance Treatment

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal After a Period of Maintenance Treatment

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

Methadose™ Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg per mL is supplied as a red, cherry-flavored liquid concentrate.

1 Liter Bottle……NDC 0406-0527-10
15 Liter Bottle.....NDC 0406-0527-15

Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg per mL is supplied as a dye-free, sugar-free, unflavored liquid concentrate.

1 Liter Bottle……NDC 0406-8725-10

15 Liter Bottle..……NDC 0406-8725-15

Dispense in tight containers, protected from light. Store at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature].

Methadose is a trademark of Mallinckrodt Inc.

Mallinckrodt Inc.

Hazelwood, MO 63042 U.S.A.

tyco

Healthcare

Mallinckrodt

Rev 101507

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBUTEX® sublingual tablet safely and effectively. See full prescribing information for SUBUTEX sublingual tablet.

SUBUTEX (buprenorphine) sublingual tablet for sublingual administration
CIII

Initial U.S. Approval: 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Patients With Hepatic Impairment (2.5)	12/2014
Warnings and Precautions, Use in Patients With Impaired Hepatic Function (5.11)	12/2014

----------INDICATIONS AND USAGE----------

SUBUTEX sublingual tablet is indicated for the treatment of opioid dependence and is preferred for induction. Prescription use of this product is limited under the Drug Addiction Treatment Act**.** (1**)**

----------DOSAGE AND ADMINISTRATION----------

Administer SUBUTEX sublingual tablet sublingually as a single daily dose. (2)

To avoid precipitating withdrawal, induction with SUBUTEX sublingual tablet should be undertaken when objective and clear signs of withdrawal are evident. (2.1). SUBOXONE® (buprenorphine and naloxone) sublingual film CIII or SUBOXONE® (buprenorphine and naloxone) sublingual tablet CIII is generally initiated after two days of SUBUTEX sublingual tablet titration.

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual tablet: 2 mg buprenorphine and 8 mg buprenorphine. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine. (4)

----------WARNINGS AND PRECAUTIONS----------

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBUTEX sublingual tablet, or both in situations of concomitant prescription. (5.3)
- Store SUBUTEX sublingual tablet safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBUTEX sublingual tablet to patients with known hypersensitivity to buprenorphine. (5.7)
- SUBUTEX sublingual tablet may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists if administered sublingually or parenterally before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBUTEX sublingual tablet is NOT appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose of buprenorphine. (5.10)
- SUBUTEX sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment(5.11)
- Caution patients about the risk of driving or operating hazardous machinery. (5.12)

----------ADVERSE REACTIONS----------

Adverse events most commonly observed during clinical trials and post-marketing experience for SUBUTEX sublingual tablet are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. (6.1 and 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088, or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBUTEX sublingual tablet for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Safety and effectiveness of SUBUTEX sublingual tablet in patients below the age of 16 have not been established. (8.4)
- Administer SUBUTEX sublingual tablet with caution to elderly or debilitated patients. (8.5)
- SUBUTEX sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: December 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections and subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBUTEX sublingual tablet is indicated for the treatment of opioid dependence and is preferred for induction. SUBUTEX sublingual tablet should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2 DOSAGE AND ADMINISTRATION

SUBUTEX sublingual tablet is administered sublingually as a single daily dose. SUBUTEX sublingual tablet contains no naloxone and is preferred for use only during induction. Following induction, SUBOXONE sublingual film or SUBOXONE sublingual tablet is preferred due to the presence of naloxone when clinical use includes unsupervised administration. The use of SUBUTEX sublingual tablet for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE sublingual film or SUBOXONE sublingual tablet; for example, those patients who have been shown to be hypersensitive to naloxone.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

2.1 Induction

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with SUBUTEX sublingual tablet should be undertaken when objective and clear signs of withdrawal are evident.

It is recommended that an adequate treatment dose, titrated to clinical effectiveness, should be achieved as rapidly as possible. In a one-month study, patients received 8 mg of SUBUTEX sublingual tablet on Day 1 and 16 mg SUBUTEX sublingual tablet on Day 2. From Day 3 onward, patients received either SUBOXONE sublingual tablet or SUBUTEX sublingual tablet at the same buprenorphine dose as Day 2 based on their assigned treatment. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose. In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period.

Patients taking heroin or other short-acting opioids:

At treatment initiation, the dose of SUBUTEX sublingual tablet should be administered at least 4 hours after the patient last used opioids or preferably when moderate objective signs of opioid withdrawal appear.

Patients on methadone or other long-acting opioids:

There is little controlled experience with the transfer of methadone-maintained patients to buprenorphine. Available evidence suggests that withdrawal signs and symptoms are possible during induction onto buprenorphine. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30 mg) and when the first buprenorphine dose is administered shortly after the last methadone dose. SUBUTEX sublingual tablet dosing should be initiated preferably when moderate

objective signs of opioid withdrawal appear.

2.2 Maintenance

- SUBOXONE is preferred for maintenance treatment.
- Where SUBUTEX is used in maintenance in patients who cannot tolerate the presence of naloxone, the dosage of SUBUTEX should be progressively adjusted in increments / decrements of 2 mg or 4 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose is generally in the range of 4 mg to 24 mg buprenorphine per day depending on the individual patient. Doses higher than this have not been demonstrated to provide any clinical advantage.

2.3 Method of Administration

SUBUTEX sublingual tablet should be placed under the tongue until it is dissolved. For doses requiring the use of more than two tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than two tablets comfortably), place two tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

Proper administration technique should be demonstrated to the patient.

2.4 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE, for example those patients with known hypersensitivity to naloxone. SUBOXONE and SUBUTEX are both subject to diversion and abuse. When determining the size of the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability of the patient to manage supplies of take-home medication.

Ideally, patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).

5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

2.5 Patients With Hepatic Impairment

Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Moderate hepatic impairment: Although no dose adjustment is necessary for patients with moderate hepatic impairment, SUBUTEX sublingual tablets should be used with caution in these patients and prescribers should monitor patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Mild hepatic impairment: No clinically significant differences in pharmacokinetic parameters were observed in subjects with mild hepatic impairment. No dose adjustment is needed in patients with mild hepatic impairment . *[see Warnings and Precautions (5.11)]*.

2.6 Unstable Patients

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.7 Stopping Treatment

The decision to discontinue therapy with SUBOXONE or SUBUTEX after a period of maintenance should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation of buprenorphine has been used, but the data are insufficient to determine the best method of dose taper at the end of treatment.

3 DOSAGE FORMS AND STRENGTHS

SUBUTEX sublingual tablet is supplied as an uncoated oval white tablet in two dosage strengths:

- buprenorphine 2 mg, and
- buprenorphine 8 mg

4 CONTRAINDICATIONS

SUBUTEX sublingual tablet should not be administered to patients who have been shown to be hypersensitive to buprenorphine, as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.7)].*

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits *[see Drug Abuse and Dependence (9.2)].*

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBUTEX sublingual tablet *[see Drug Interactions (7.3)].*

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

SUBUTEX sublingual tablet should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBUTEX sublingual tablet, or both in situations of concomitant prescription *[see Drug Interactions (7.3)].*

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children and destroy any unused medication appropriately *[see Patient Counseling (17)].*

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion *[see Drug Abuse and Dependence (9.3)].*

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports

of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBUTEX sublingual tablet may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneutrotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine is a contraindication to the use of SUBUTEX sublingual tablet.

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because of the partial agonist properties of buprenorphine, SUBUTEX sublingual tablet may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists if administered sublingually or parenterally before the agonist effects of other opioids have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs and symptoms ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus and there have been reports of convulsions, apnea, respiratory depression and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBUTEX sublingual tablet is not appropriate as an analgesic.

5.11 Use in Patients With Impaired Hepatic Function

In a pharmacokinetic study, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment.

For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*.

5.12 Impairment of Ability to Drive or Operate Machinery

SUBUTEX sublingual tablet may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that buprenorphine therapy does not adversely affect his or her ability to engage in such activities.

5.13 Orthostatic Hypotension

Like other opioids, SUBUTEX sublingual tablet may produce orthostatic hypotension in ambulatory patients.

5.14 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.15 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.16 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.17 General Precautions

SUBUTEX sublingual tablet should be administered with caution in debilitated patients and those with myxedema or hypothyroidism; adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Events in Clinical Trials

The safety of SUBUTEX sublingual tablet was supported by clinical trials using SUBUTEX sublingual tablet, SUBOXONE (buprenorphine/naloxone sublingual tablet) and other trials using buprenorphine sublingual solutions. In total, safety data were available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction.

Few differences in adverse event profile were noted between SUBUTEX or buprenorphine administered as a sublingual solution.

The following adverse events were reported to occur by at least 5% of patients in a 4-week study (Table 1).

Table 1. Adverse Events ≥ 5% by Body System and Treatment Group in a 4-week study		
	N (%)	N (%)
Body System / Adverse Event (COSTART Terminology)	**SUBUTEX 16 mg/day N=103**	**Placebo N=107**
Body as a Whole		
Asthenia	5 (4.9%)	7 (6.5%)
Chills	8 (7.8%)	8 (7.5%)
Headache	30 (29.1%)	24 (22.4%)
Infection	12 (11.7%)	7 (6.5%)
Pain	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.7%)	7 (6.5%)
Pain Back	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	19 (18.4%)	40 (37.4%)
Cardiovascular System		
Vasodilation	4 (3.9%)	7 (6.5%)
Digestive System		
Constipation	8 (7.8%)	3 (2.8%)
Diarrhea	5 (4.9%)	16 (15.0%)
Nausea	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.8%)	5 (4.7%)
Nervous System		
Insomnia	22 (21.4%)	17 (15.9%)
Respiratory System		
Rhinitis	10 (9.7%)	14 (13.1%)
Skin And Appendages		
Sweating	13 (12.6%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. Table 2 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

Table 2. Adverse Events (≥ 5%) by Body System and Treatment Group in a 16-week Study					
Body System /Adverse Event (COSTART Terminology)	**Buprenorphine Dose***				
	Very Low* (N=184)	**Low* (N=180)**	**Moderate* (N=186)**	**High* (N=181)**	**Total* (N=731)**
	N (%)	N (%)	N (%)	N (%)	N (%)
*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes: "Very low" dose (1 mg solution) would be less than a tablet dose of 2 mg "Low" dose (4 mg solution) approximates a 6 mg tablet dose "Moderate" dose (8 mg solution) approximates a 12 mg tablet dose "High" dose (16 mg solution) approximates a 24 mg tablet dose					
Body as a Whole					
Abscess	9 (5%)	2(1%)	3 (2%)	2(1%)	16(2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10(5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186(25%)
Nervousness	12 (7%)	11 (6%)	10(5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)

Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin And Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

6.2 Adverse Events - Post-marketing Experience with SUBUTEX Sublingual Tablets

The most frequently reported post-marketing adverse events with SUBUTEX not observed in clinical trials, excluding drug exposure during pregnancy, was drug misuse or abuse.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBUTEX sublingual tablet is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBUTEX sublingual tablet with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with many CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBUTEX sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. *[see Clinical Pharmacology (12.3)]*

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBUTEX sublingual tablet should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBUTEX sublingual tablet, and should also be cautioned to use benzodiazepines concurrently with SUBUTEX sublingual tablet only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies of SUBUTEX tablets or buprenorphine in pregnant women. Limited published data on use of buprenorphine, the active ingredient in SUBUTEX, in pregnancy, have not shown an increased risk of major malformations. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss. Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre-and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. Embryofetal death was also observed in both rats and rabbits.

SUBUTEX tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Opioid dependence in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death.

Fetal/neonatal adverse reactions

Neonatal abstinence syndrome may occur in newborn infants of mothers who were on buprenorphine maintenance treatment. Observe newborns for poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see Warnings and Precautions (5.9)].

Labor or Delivery

As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn.

Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.

Data

Human Data

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of neonatal abstinence syndrome is not clear and there does not appear to be a dose-response relationship.

Animal Data:

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri- and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

8.3 Nursing Mothers

Risk Summary

Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is minimal. Caution should be exercised when SUBUTEX is administered to a nursing woman. The developmental and health benefits of breastfeeding

should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Advise the nursing mother taking SUBUTEX to monitor the infant for increased drowsiness and breathing difficulties.

Data

Based on limited data from a study of 6 lactating women who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose.

Based on limited data from a study of 7 lactating women who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

No adverse reactions were observed in the infants in these two studies.

8.4 Pediatric Use

The safety and effectiveness of SUBUTEX sublingual tablet has not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBUTEX sublingual tablet, SUBOXONE sublingual film, or SUBOXONE sublingual tablet did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study. Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment.

For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.
[see Dosage and Administration (2.5), Warnings and Precautions (5.11) and Clinical Pharmacology (12.3)].

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert, buprenorphine products or other opioids should be provided or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. *[see Warnings and Precautions (5.5)]*

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy. *[see Warnings and Precautions (5.9)]*

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

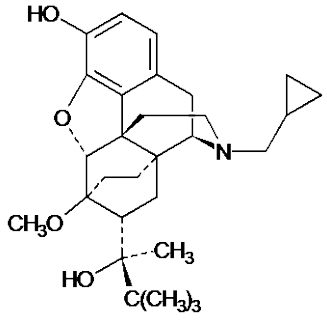
In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. The long duration of action of SUBUTEX should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an

overdose. Insufficient duration of monitoring may put patients at risk.

11 DESCRIPTION

SUBUTEX (buprenorphine) sublingual tablet is an uncoated oval white tablet, imprinted with a sword logo on one side and an alphanumeric imprint identifying the product and strength. It contains buprenorphine HCl and is available in two dosage strengths, 2 mg buprenorphine and 8 mg buprenorphine (as free base). Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate.

Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



• HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4$ • HCl and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBUTEX sublingual tablet contains buprenorphine. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

12.2 Pharmacodynamics

***Subjective Effects**:*

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

12.3 Pharmacokinetics

Absorption:

Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX sublingual tablet (Table 3). There was wide inter-patient variability in the sublingual absorption of buprenorphine, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

Table 3. Pharmacokinetic Parameters of Buprenorphine and Norbuprenorphine after the sublingual administration of SUBUTEX sublingual tablets

Dose	Analyte	Mean SD	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (h•ng/mL)	$t_{1/2}$ (h)
2 mg[a]	Buprenorphine	Mean SD	1.25 0.584	1.84 0.62	10.93 3.945	31.66 12.66
	Norbuprenorphine	Mean SD	0.301 0.127	2.36 2.75	12.39 4.526	39.28 20.85
8 mg[b]	Buprenorphine	Mean SD	2.88 1.14	1.28 0.46	28.39 10.22	35.01 14.7
	Norbuprenorphine	Mean SD	1.38 0.752	1.75 2.11	50.18 22.61	44.33 19.27
16 mg[c]	Buprenorphine	Mean SD	4.70 2.16	1.42 0.50	47.09 20.03	36.51 13.99
	Norbuprenorphine	Mean SD	2.65 1.62	1.52 1.34	92.31 34.74	40.35 12.07

[a] *Source: Study Report 20-A78-AU*
[b] *Source: Study Report 20-276-SA*
[c] *Source: Study Report 20-A79-AU*

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma ranging from 31 to 35 hours.

Drug-drug interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBUTEX sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBUTEX sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[see Drug Interactions (7.1)].*

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

Special Populations:

Hepatic Impairment: In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg SUBOXONE (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant. No dose adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were increased (Table 4). *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.6)]*.

Table 4. Changes in Buprenorphine Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects
Moderate	C_{max}	8%
	$AUC_{0\text{-last}}$	64%
	Half-life	35%
Severe	C_{max}	72%
	$AUC_{0\text{-last}}$	181%
	Half-life	57%

HCV infection: In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection. No dose adjustment is needed in patients with HCV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity:

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

14 CLINICAL STUDIES

Clinical data on the safety and efficacy of SUBUTEX were derived from studies of buprenorphine sublingual tablet formulations, with and without naloxone, and from studies of sublingual administration of a more bioavailable ethanolic solution of buprenorphine.

SUBUTEX tablets were studied in 1834 patients; SUBOXONE tablets (buprenorphine with naloxone) in 575 patients, and buprenorphine sublingual solutions in 2470 patients. A total of 1270 women received buprenorphine in those clinical trials. Dosing recommendations are based on data from one trial of both tablet formulations and two trials of the ethanolic solution. All trials used buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. There were no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

In a double-blind placebo- and active-controlled study, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE sublingual tablets, 16/4 mg per day; SUBUTEX sublingual tablets, 16 mg per day; or placebo sublingual tablets. For subjects randomized to either active treatment, dosing began with one 8 mg SUBUTEX on Day 1, followed by 16 mg (two 8 mg tablets) of SUBUTEX on Day 2. On Day 3, those randomized to receive SUBOXONE sublingual tablets were switched to the combination tablet. Subjects randomized to placebo received one placebo tablet on Day 1 and two placebo tablets per day thereafter for four weeks. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. Subjects were instructed to hold the medication under the tongue for approximately 5 to 10 minutes until completely dissolved. Subjects received counseling regarding HIV infection and up to one hour of individualized counseling per week. The primary study comparison was to assess the efficacy of SUBOXONE sublingual tablets and SUBUTEX sublingual tablets individually against placebo sublingual tablet. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBOXONE sublingual tablets and SUBUTEX sublingual tablets than for placebo sublingual tablets.

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg per day of SUBUTEX sublingual tablets), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3-10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually.

Maintenance dosing continued through Week 17, and then medications were tapered by approximately 20%-30% per week over Weeks 18-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counseling weekly.

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of

buprenorphine, 8mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

In a dose-controlled, double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution: 1 mg, 4 mg, 8 mg, and 16 mg. Buprenorphine was titrated to maintenance doses over 1-4 days and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site.

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested doses were superior to the 1 mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1 mg dose of buprenorphine sublingual solution can be considered to be somewhat lower than a 2 mg tablet dose. The other doses used in the study encompass a range of tablet doses from approximately 6 mg to approximately 24 mg.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBUTEX sublingual tablet is an uncoated oval white tablet, imprinted with a sword logo on one side and an alphanumeric imprint identifying the product and strength on the other side, supplied in white HDPE bottles:

- NDC 12496-1278-2 (buprenorphine 2 mg/sublingual tablet; content expressed in terms of free base) - 30 tablets per bottle
- NDC 12496-1310-2 (buprenorphine 8 mg/sublingual tablet; content expressed in terms of free base) - 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F). [see USP Controlled Room Temperature].

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children. Destroy any unused medication appropriately. *[see Patient Counseling (17)]* Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Safe Use

Before initiating treatment with SUBUTEX sublingual tablet, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBUTEX sublingual tablet is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBUTEX sublingual tablet. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physicians *[see Warnings and Precautions (5.2), Drug Interactions (7.3)].*
- Patients should be advised that SUBUTEX sublingual tablet contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their tablets in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBUTEX sublingual tablet in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory

depression that can result in death. Patients should be advised that if a child is exposed to SUBUTEX sublingual tablet, medical attention should be sought immediately.

- Patients should be advised never to give SUBUTEX sublingual tablet to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBUTEX sublingual tablet may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating hazardous machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.12)].*
- Patients should be advised not to change the dosage of SUBUTEX sublingual tablet without consulting their physicians.
- Patients should be advised to take SUBUTEX sublingual tablet once a day.
- Patients should be informed that SUBUTEX sublingual tablet can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physicians on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should be cautioned that, like other opioids, SUBUTEX sublingual tablet may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions (5.13)].*
- Patients should inform their physicians if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used *[see Drug Interactions (7.1, 7.2 and 7.3)].*
- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBUTEX sublingual tablet during pregnancy *[see Specific Populations (8.1)].*
- Patients should be warned that buprenorphine passes into breast milk. Breast-feeding is therefore not advised in mothers treated with buprenorphine products *[see Specific Populations (8.3)].*
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBUTEX sublingual tablet.
- Refer to the Medication Guide for additional information regarding the counseling information.

Disposal of Unused SUBUTEX Sublingual Tablets

Unused SUBUTEX sublingual tablets should be disposed of as soon as they are no longer needed. Flush unused tablets down the toilet.

Manufactured by:

Reckitt Benckiser Healthcare (UK) Ltd.

Hull, UK, HU8 7DS

Distributed by:

Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235

MEDICATION GUIDE

SUBUTEX® (Sub-u-tex)
(buprenorphine)
Sublingual Tablet (CIII)

IMPORTANT:

Keep SUBUTEX in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses SUBUTEX, get emergency help right away.

Read this Medication Guide before you start taking SUBUTEX and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor. Talk to your doctor or pharmacist if you have questions about SUBUTEX.

Share the important information in this Medication Guide with members of your household.

What is the most important information I should know about SUBUTEX sublingual tablets?

- SUBUTEX can cause serious and life-threatening breathing problems. Call your doctor right away or get emergency help if:
  - You feel faint, dizzy or confused
  - Your breathing gets much slower than is normal for you

  These can be signs of an overdose or other serious problems.
- SUBUTEX contains an opioid that can cause physical dependence.
  - Do not stop taking SUBUTEX without talking to your doctor. You could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine
  - Physical dependence is not the same as drug addiction
  - SUBUTEX is not for occasional or "as needed" use
- An overdose, and even death, can happen if you take benzodiazepines, sedatives, tranquilizers, or alcohol while using SUBUTEX. Ask your doctor what you should do if you are taking one of these.
- Call a doctor or get emergency help right away if you:
  - Feel sleepy and uncoordinated
  - Have blurred vision
  - Have slurred speech
  - Cannot think well or clearly
  - Have slowed reflexes and breathing
- Do not inject ("shoot-up") SUBUTEX.

- Injecting this medicine may cause life-threatening infections and other serious health problems.
- Injecting SUBUTEX may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems and cravings.

- In an emergency, have family members tell the emergency department staff that you are physically dependent on an opioid and are being treated with SUBUTEX.

What is SUBUTEX sublingual tablet?

- SUBUTEX is a prescription medicine used to begin treatment in adults who are addicted to (dependent on) opioid drugs (either prescription or illegal drugs), as part of a complete treatment program that also includes counseling and behavioral therapy.
- SUBUTEX is most often used for the first 1 or 2 days to help you start with treatment.

SUBUTEX is a controlled substance (CIII) because it contains buprenorphine, which can be a target for people who abuse prescription medicines or street drugs. Keep your SUBUTEX in a safe place to protect it from theft. Never give your SUBUTEX to anyone else; it can cause death or harm them. Selling or giving away this medicine is against the law.

- It is not known if SUBUTEX is safe or effective in children.

Who should not take SUBUTEX sublingual tablets?

Do not take SUBUTEX if you are allergic to buprenorphine.

What should I tell my doctor before taking SUBUTEX sublingual tablets?

SUBUTEX may not be right for you. Before taking SUBUTEX, tell your doctor if you:

- Have trouble breathing or lung problems
- Have an enlarged prostate gland (men)
- Have a head injury or brain problem
- Have problems urinating
- Have a curve in your spine that affects your breathing
- Have liver or kidney problems
- Have gallbladder problems
- Have adrenal gland problems
- Have Addison's disease
- Have low thyroid (hypothyroidism)
- Have a history of alcoholism
- Have mental problems such as hallucinations (seeing or hearing things that are not there)
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if SUBUTEX will harm your unborn baby. If you take SUBUTEX while pregnant, your baby may have symptoms of withdrawal at birth. Talk to your doctor if you are pregnant or plan to

become pregnant.
- Are breast feeding or plan to breast feed. SUBUTEX can pass into your milk and may harm the baby. Talk to your doctor about the best way to feed your baby if you take SUBUTEX. Breast feeding is not recommended while taking SUBUTEX.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements. SUBUTEX may affect the way other medicines work, and other medicines may affect how SUBUTEX works. Some medicines may cause serious or life-threatening medical problems when taken with SUBUTEX.

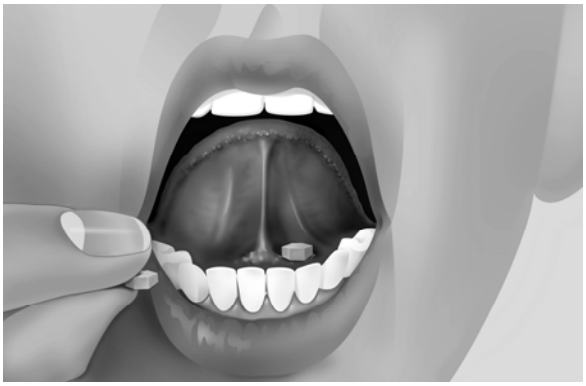
Sometimes the doses of certain medicines and SUBUTEX may need to be changed if used together. Do not take any medicine while using SUBUTEX until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using SUBUTEX.

Be especially careful about taking other medicines that may make you sleepy, such as pain medicines, tranquilizers, sleeping pills, anxiety medicines or antihistamines.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist each time you get a new medicine.

How should I take SUBUTEX sublingual tablets?

- Always take SUBUTEX exactly as your doctor tells you**.** Your doctor may change your dose after seeing how it affects you. Do not change your dose unless your doctor tells you to change it.
- Do not take SUBUTEX more often than prescribed by your doctor.
- If you are prescribed a dose of 2 or more SUBUTEX tablets at the same time:
  - Ask your doctor for instructions on the right way to take SUBUTEX tablets
  - Follow the same instructions every time you take a dose of SUBUTEX tablet
- Put the tablets under your tongue. Let them dissolve completely.



- While SUBUTEX is dissolving, do not chew or swallow the tablet because the medicine will not work as well.
- Talking while the tablet is dissolving can affect how well the medicine in SUBUTEX is

absorbed.

- If you miss a dose of SUBUTEX, take your medicine when you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time unless your doctor tells you to. If you are not sure about your dosing, call your doctor.
- Do not stop taking SUBUTEX suddenly. You could become sick and have withdrawal symptoms because your body has become used to the medicine. Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction. To have fewer withdrawal symptoms, ask your doctor how to stop using SUBUTEX the right way.
- **If you take too much SUBUTEX or overdose, call Poison Control or get emergency medical help right away.**

What should I avoid while taking SUBUTEX sublingual tablets?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how this medication affects you.** Buprenorphine can cause drowsiness and slow reaction times. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative drugs when you take SUBUTEX.
- **You should not drink alcohol** while using SUBUTEX, as this can lead to loss of consciousness or death.

What are the possible side effects of SUBUTEX sublingual tablets?

SUBUTEX can cause serious side effects including:

- **See "What is the most important information I should know about SUBUTEX sublingual tablets?"**
- **Respiratory problems.** You have a higher risk of death and coma if you take SUBUTEX with other medicines, such as benzodiazepines.
- **Sleepiness, dizziness, and problems with coordination**
- **Dependency or abuse**
- **Liver problems.** Call your doctor right away if you notice any of these signs of liver problems: Your skin or the white part of your eyes turning yellow (jaundice), urine turning dark, stools turning light in color, you have less of an appetite, or you have stomach (abdominal) pain or nausea. Your doctor should do tests before you start taking and while you take SUBUTEX.
- **Allergic reaction.** You may have a rash, hives, swelling of your face, wheezing, or loss of blood pressure and consciousness. Call a doctor or get emergency help right away.
- **Opioid withdrawal.** This can include: shaking, sweating more than normal, feeling hot or cold more than normal, runny nose, watery eyes, goose bumps, diarrhea, vomiting and muscle aches. Tell your doctor if you develop any of these symptoms.
- **Decrease in blood pressure.** You may feel dizzy if you get up too fast from sitting or lying down.

Common side effects of SUBUTEX sublingual tablets include:

- Headache
- Nausea
- Vomiting
- Increased sweating
- Constipation
- Drug withdrawal syndrome
- Decrease in sleep (insomnia)
- Pain

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects of SUBUTEX sublingual tablet. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SUBUTEX sublingual tablets?

- Store SUBUTEX between 59°F and 86°R (15°C to 30°C).
- **Keep SUBUTEX in a safe place, out of the site and reach of children.**

How should I dispose of unused SUBUTEX sublingual tablets?

- Dispose of unused SUBUTEX sublingual tablets as soon as you no longer need them.
- Flush unused tablets down the toilet.

General information about the safe and effective use of SUBUTEX sublingual tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SUBUTEX for a condition for which it was not prescribed. Do not give SUBUTEX to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about SUBUTEX sublingual tablet. If you would like more information, talk to your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

For more information call 1-877-782-6966.

What are the ingredients in SUBUTEX sublingual tablets?

Active Ingredient: buprenorphine
Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, and magnesium stearate

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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